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CELL PATHOLOGY AND AGEING

CELLULAR RESPONSE

Stimuli

1. Altered Physiologic stimuli OR Non-Lethal Stimuli } CELLUR ADAPTATION
   Eg : i) Atrophy
   ii) Hypertrophy
   iii) Hyperplasia
   iv) Metaplasia
2. Lethal Stimuli - Transient : Reversible Cell injury
   Lethal Stimuli - Persistent : Irreversible injury
   ↓
   Cell death
   ↓
   MORPHOLOGICAL CHANGES : NECROSIS, APOPTOSIS, NECROPTOSIS, PYROPTOSIS
3. Chronic Injury Stimuli : Intracellular accumulation
   Eg : Fats, Glycogen, Proteins
   ⇒ Calcification
4. Sublethal Stimuli : Persistent : Induce Cellular ageing

CELLULAR ADAPTATIONS

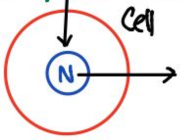
- Stimuli ⟶ Cell ⟶ Change in their Number, Size, Phenotype, functions
  ↓
  Removal ⟶ Comeback to Ⓝ State
  ∴ CELLULAR ADAPTATIONS ARE REVERSIBLE
- These are both Physiologic & Pathologic
  Physiologic ↓ Pregnant Uterus
  Pathologic ↓ Barrett's Esophagus

HYPERTROPHY

- definition : Size of cell ↑ but Number of cell same
- Mechanism : ↑ in synthesis of cellular protein
- Is also both Physiological & Pathological
  Physiological ↓ Eg : Pregnant uterus (both hypertrophy & hyperplasia)
  Pathological ↓ Eg : Cardiac Enlargement d/t Valvular defect.

HYPERPLASIA

- def : No. of cell Increased. But size of cell remains same
- Mechanism : i) ↑ Growth Factor : Most important mechanism



→ ↑ Nu. Transcription Factor
↓
↑ Cell proliferation

ii) ↑ tissue stem cells
↓
↑ no. of cells

- Both Physiologic & Pathological

Physiologic ↓
- Pregnant uterus
- Pregnant Breast
- Compensatory Hyperplasia
  - → Liver regeneration after Liver Resection

Pathological ↓
- ↑↑ Estrogen on the endometrium
  ↓
  Endometrial Hyperplasia

ATROPHY

- def : Size & no. of cell are decreased.
- Mechanisms : i) ↓ protein synthesis
  ii) Ubiquitin Proteasome Degradation pathway ⟷ iii) Autophagy

Autophagy → Self ↓ Eating ↓

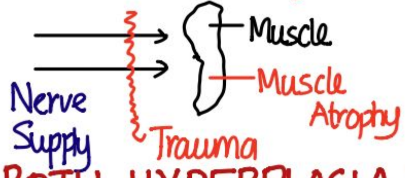
INTRACELLULAR PROTEIN DEGRADATION PATH WAY

Ubiquitin - Ligase activation
⇓
Ubiquitin
+
Target protein
↓

⊕ ↓ Activate proteasome (organelle)
⇓
degradation of Ubiquitin + Tar. protein
⇓
ATROPHY

These are taken into ↓
Double membrane bound Autophagosome
(Contain Ubi + Tar. pro)
↓
Combine with Lysosome
⇓
Degradation of Protein

- Both **Physiologic** & **Pathological**
  - Physiologic ↓ during fetal development ⇓ loss of notochord & Thyroglossal duct
  - Pathological ↓ Denervation atrophy

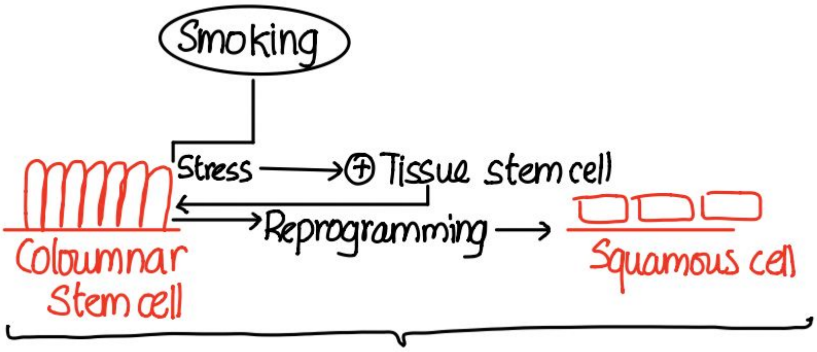


- Endometrial Adenocarcinoma a/w BOTH HYPERPLASIA & ATROPHY
  - HYPERPLASIA ↓ a/w Type-1 Endometrial Adenocarcinoma → Good Prognosis
  - ATROPHY ↓ a/w Type-2 Endo Adenocarcinoma → Poor prognosis
  - ∴ Both are precancerous lesion

METAPLASIA

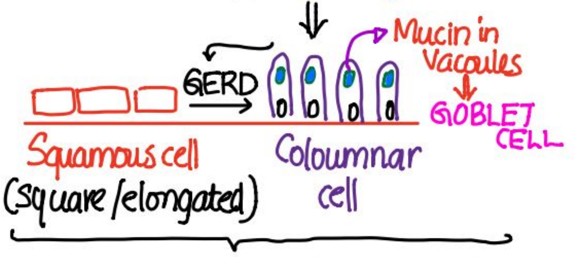
- def : 1 mature cell replaced by another type of mature cell
- Mechanism : CYTOKINE / GF ↓ Alteration of tissue-stem cell Reprogramming
- Both **Physiologic** & **Pathologic**
  - Physiologic ↓ In cervix (during menustruation) Squamous metaplasia at squamo coloumnar junction
  - Pathologic
    - EPITHELIAL
    - CONNECTIVE TISSUE/ MESENCHYMAL META.
      Eg : Myositis ossificans
      Trauma → Mus. inj ↓ Bone within muscle

- MC Type :



Squamous Metaplasia of Resp. Tract
(MC Type of metaplasia)
# d/t Vitamin A deficiency
Vitamin A excess

- BARRETT'S EOSOPHAGUS
  - MCC : Gastro eosophageal Reflux Disease (GERD) ⇓



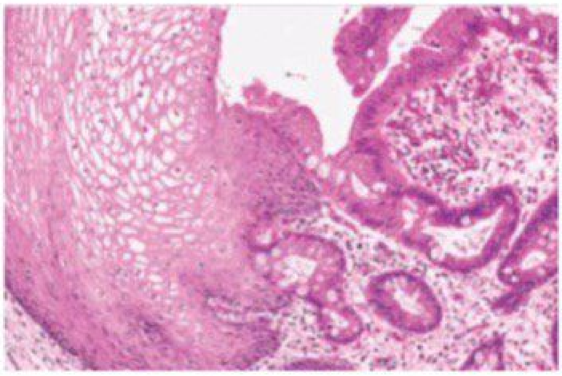
Coloumnar Metaplasia
- d/t to the presence of GOBLET CELL aka INTESTINAL METAPLASIA (Hallmark of Barret's E.)
- Stain for GOBLET CELL :
  Alcian Blue Stain : pH = 2·5 (acidic)
  for intestinal Goblet : pH = alkaline

Risk of Barret's Esophagus : Adenocarcinoma of Esophagus

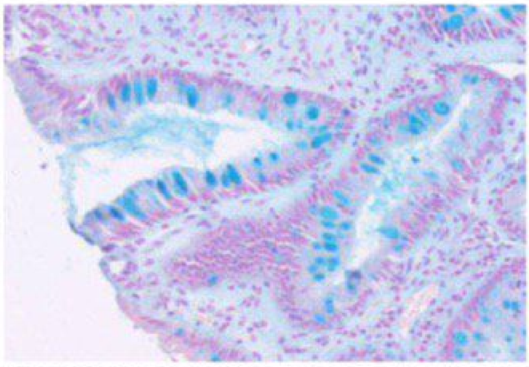
Metaplasia ⟶ Dysplasia ⟶ Carcinoma

↓

Exception : Apocrine metaplasia of breast tissue have no risk of malignancy



BARRETT'S ESOPHAGUS
Showing squamous to columnar metaplasia (Columnar metaplasia).



ALCIAN BLUE STAIN OF BARRETT'S MUCOSA:
shows the blue-staining goblet cells, a few specialized columnar cells, and the clear-staining gastric-type surface columnar cells

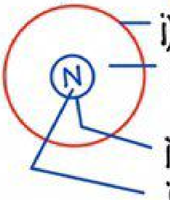
CELL - INJURY

- MCC of cell injury : ISCHAEMIA
↓
HYPOXIA ⟶ OXIDATIVE STRESS on mitochondria
↓
Free radicals production

FREE RADICALS

aka = Oxidants
= Reactive oxygen species (ROS)

- FR are normally produced d/t incomplete oxidation within mitochondria
- Def : Any chemical species with unpaired e⁻ (outer orbit)
- Mechanism of action : by oxidative damage
↓



Damage of
i) Cell membrane
ii) Cytoplasmic proteins/organelle
iii) Nu. membrane
iv) Nu. chromatin/DNA damage

FREE-RADICAL (Oxidant)	Anti-Oxidant
i) $OH^{\bullet}$: MOST REACTIVE	i) Vitamins : A / C / E
ii) H_2O_2	ii) Proteins : Transferrin, Ceruloplasmin
iii) $O_2^{\bullet}$	iii) Enzymes : Catalase, Glutathione SOD (Superoxide dismutase)
iv) $ONOO^-$	

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# 1. Catalase
2. Glutathione : MOST POTENT ANTIOXIDANT } PEROXISOMAL ENZYMES
3. SOD
→ Responsible for Brain protection from FR damage
→ Mutation in SOD gene : Amyotrophic Lateral Sclerosis (Motor neuron disease)

*** HYPOXIA

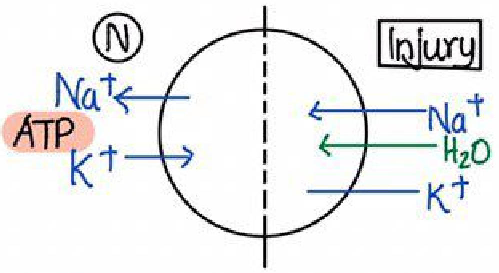
↳ Most - susceptible
- NEURONS : Survival time 3-4 min
- CARDIAC : 20-40 min (~30 min)
- FIBROBLAST : hrs to days

Types of Cell injury

- Transient stimuli
  Reversible injury
- Persistent stimuli
  Irreversible Injury

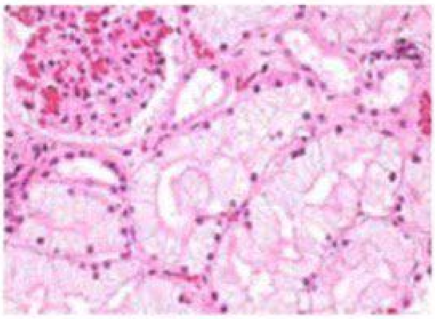
REVERSIBLE INJURY

Ischaemia (↓O_2)
↓
↓ oxidative phosphorylation in mitochondria
↓
↓ ATP production
(↓ 5-10 % of Normal)



⟹ ① First Sign : Cell Swelling
except for Apoptosis
↳ First Sign : Cell Shrinkage

② Vacuolar Degeneration/
Hydropic Degeneration
- d/t intracellular water accumulation
- aka CLOUDY SWELLING
  Eg : Acute Tubular necrosis of Kidney

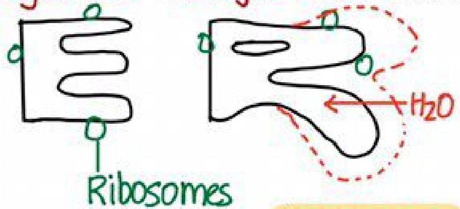


HYDROPIC CHANGE OR CLOUDY SWELLING

Sign of reversible injury due to cytoplasmic distension by excessive water entry.

③ Organelle changes : EM Examination

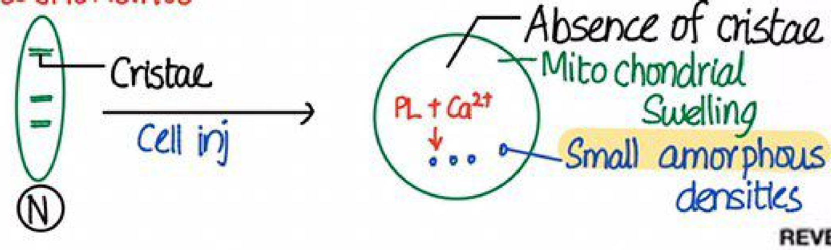
i)

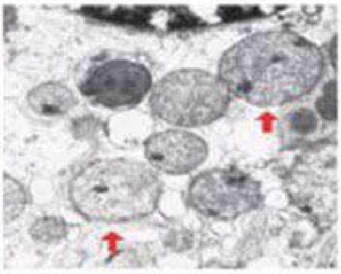


ER Swelling

ii) Ribosomal detachment

iii) Mitochondria

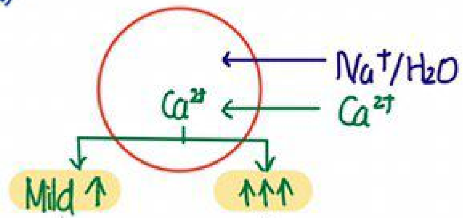




REVERSIBLE INJURY :
Electron microscopy (Ultrastructurally) showing markedly swollen mitochondria containing small amorphous densities made up of electron-dense deposits consisting of calcium and proteins.

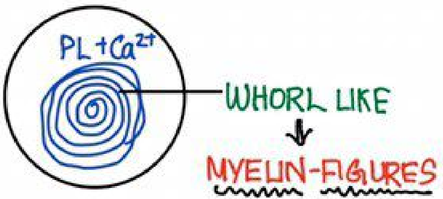
# M. Important Factor for cell injury : Ca^{2+} (Cytosolic Ca^{2+})

iv)

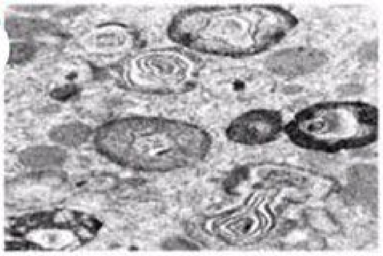


Mild ↑ → Reversible
↑↑↑ → Irreversible

Reversible
⇓
Cytosolic Ca^{2+} (mild ↑)
⇓ ⊕
Phospholipase
↓
PL (on cell membrane)

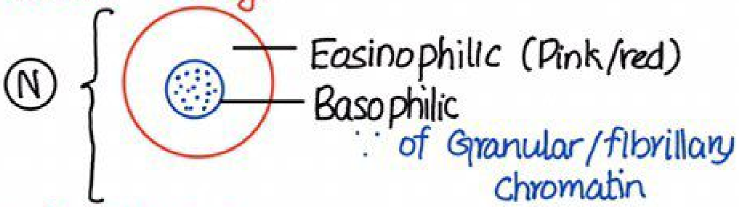


WHORL LIKE
⇓
MYELIN-FIGURES
↓
made up of PL + Ca^{2+}
seen in both reversible & irreversible injury (MC)



MYELIN FIGURES
Electron microscopy (Ultrastructurally) showing myelin figures derived from damage of the cell membrane (whorls of lamellated phospholipid and calcium).

# Nucleus - damage



In Reversible injury
i. Dis aggregation of granular/fibrillary Nu. chromatin

IRREVERSIBLE INJURY

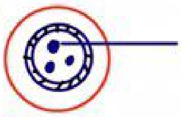
- because of Persistent lethal stimuli
⇓
↑↑ Cytosolic Ca^{2+}
↓ ⊕/Activates

Phospholipase
⇓
Cell-membrane damage
↓
i. ↑↑ Myelin figures (max)
ii. EM : Large, flocculent, amorphous densities in mitochondria

Proteases
⇓
damage of cytoskeleton protein
⇓
Loss of cell architecture

Endonuclease
⇓
Nu - damage
↓
DNA (chromatin)
i) Pyknosis
ii) Karyo-rrhexis
iii) Karyo-lysis
} SEQUENTIAL DAMAGE

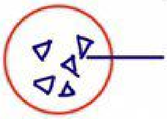
i) PYKNOSIS :



Clumping / Condensation of chromatin
+
Shrinkage of Nucleus

↓

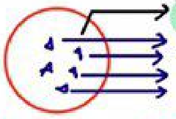
ii) Karyo-rrhexis : Nuclear fragmentation



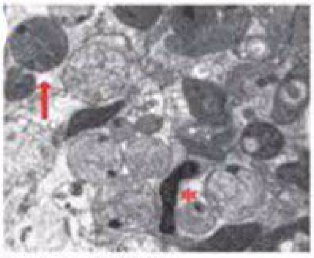
Fragmented nuclei

↓

iii) Karyolysis : Chromatin Lysis & dissolution



decreased basophilia
Thrown out



IRREVERSIBLE INJURY

Electron microscopy (Ultrastructurally) showing markedly swollen mitochondria containing large flocculent amorphous densities made up of electron-dense deposits consisting of calcium and proteins.

Irreversible injury → Cell death
↓
Morphological changes

- Necrosis
- Apoptosis
- Necroptosis
- Pyroptosis

NECROSIS

- 2 patterns of Necrosis

i. COAGULATIVE NECROSIS

* MC pattern of necrosis
⇒ Denaturation of Protein
↓
Tissue architecture : Preserved
Eg : • Ischaemic infarction of solid organs Eg : Heart (MC)
Kidney
Liver

EXCEPT IN BRAIN : Ischaemic infarction

ii. LIQUEFACTIVE NECROSIS

⇒ d/t ↑ Lysosomal permeability
↓
Enzymes leak out
↓
Enzymatic damage of cell.
(HYDROLYTIC DAMAGE)
⇒ Tissue architecture : Lost

Eg i) Ischaemic infarction of Brain
∵ there is no stromal support
∵ of absence of collagen
also brain is rich in Liquefactive enzymes
ii) Infections

SPECIAL TYPES

1. GANGRENE
- MC site : LOWER LIMB

ⓐ Dry gangrene
* tissue architecture is presevered
∴ Eg of Coagulative necrosis

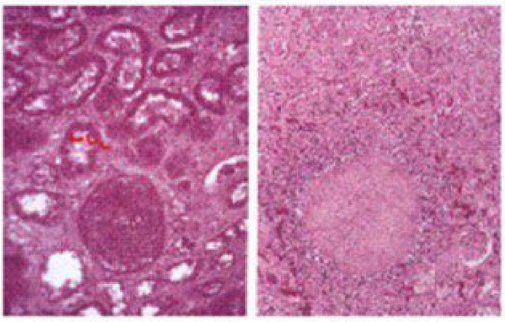
ⓑ Wet gangrene
* Bacterial contamination ⇒ Toxin / Enzyme release
* Type of Liquefactive necrosis

2. CASEOUS NECROSIS

- It's called like this ∵ of cheesy appearance : Gross
  → Yellowish-White debris
- Seen in TB : Cheesy d/t presence of MYCOLIC ACID
- On microscopic examination : Coagulative & Liquefactive Necrosis
  → Amorphous, Granular, Pink structure

considered as Variant of Coagulative Necrosis

KIDNEY



Coagulative Necrosis   Liquefactive Necrosis

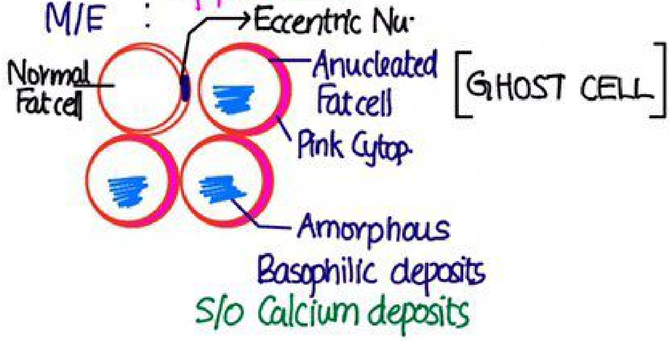
3. FAT NECROSIS

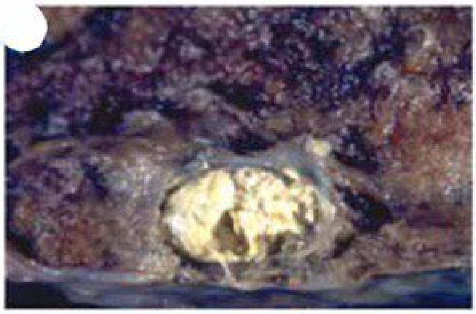
It may be due to

a) Enzymes
Acute pancreatitis
↓
Lipase released
↓
act on Lipids
↓
Release FA & combine with Ca^{2+}
called Saponification
∴ GROSS : Chalky white appearance

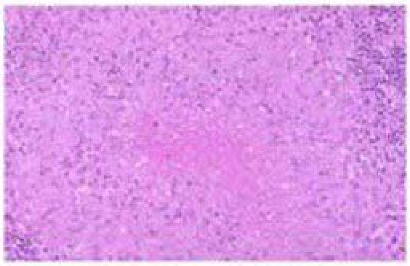
b) Trauma
Eg Breast inj.

M/E :



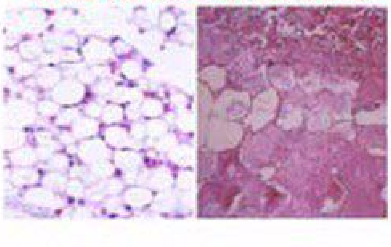


CASEOUS NECROSIS (GROSS).
Lung Tuberculosis with caseous necrosis consisting of yellow-white and cheesy debris.

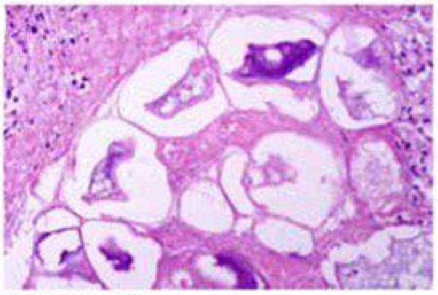


CASEOUS NECROSIS (MICROSCOPY)
Lung Tuberculosis with eosinophilic caseous necrosis and epithelioid cells.

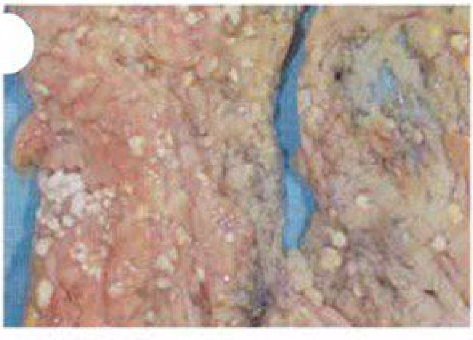
Normal Fat tissue Vs. Fat necrosis



FAT NECROSIS
Normal fat cells with eccentric nuclei is seen in image (a). Image (b) shows fat necrosis where anucleated ghost cells are seen



FAT NECROSIS
Showing Amorphous basophilic calcium deposits within cells having fat necrosis.

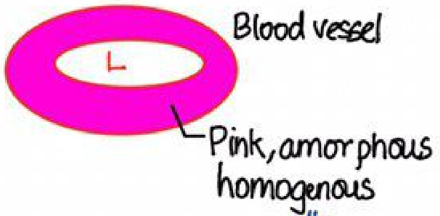


FAT NECROSIS
showing Chalky white necrosis.

5. FIBRINOID NECROSIS

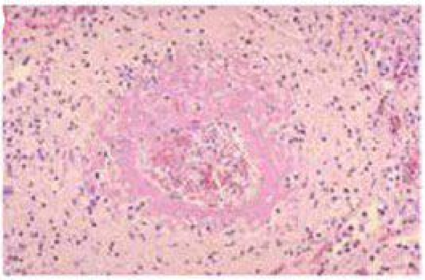
- Presence of Fibrin + Immune Complex [Ag + Ab]
- Pathology : Vessel wall damage
  ↓ ⊕
  Coagulation pathway → Fibrin formation

- Seen in i. Vasculitis : Polyarteritis Nodosa
  ii. Malignant HTN
- M/E



⇓

FIBRINOID NECROSIS



FIBRINOID NECROSIS

Showing deposition of fibrin (pink material) on the wall of arteriole as a consequence of malignant hypertension.

NECROSIS	APOPTOSIS
* ↑ Lysosomal permeability ↓ Enzymes ↓ Cell membrane damage ↓ IC content leak outside & acts as chemoattractant ↓ INFLAMMATION	* d/t ↑ mitochondrial permeability ↓ Intact Cell membrane intact ∴ No leacking ↓ ∴ NO INFLAMMATION
* Always pathological	* Apoptosis both physiological & pathological.

APOPTOSIS

- falling - off the cells from the tissue (literal meaning)
- Programmed Cell death is seen in
  i. Apoptosis
  ii. Necroptosis
  iii. Pyroptosis
  iv. Neutrophilic Extracellular Trap (NET)
- Energy depend. process ≫ Programmed Cell Death
  (active process)
- Apoptosis is PHYSIOLOGICAL (MC) ↓

Eg: 1. Organogenesis / Embryogenesis
2. Neo vascularisation
3. Killing of inflammatory cells after completing their function
4. Elimination of auto-reactive cell (to prevent Auto immunity)

PATHOLOGICAL ↓

Eg 1. Chemotherapy or Radio therapy (Apoptosis + Necrosis)
2. Glucorticoid induce apoptosis (∵ prevent autoimmu)
3. Graft v/s Host disease
4. Councilman bodies in Vira Hepatitis. These are apoptotic bodies
5. Misfolding of protein

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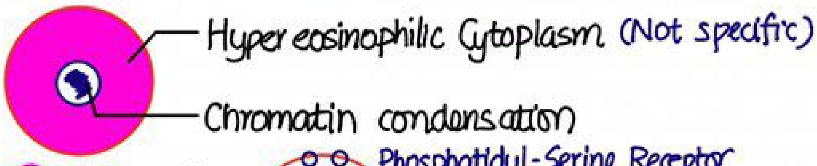
- MORPHOLOGY :
  - a. Cell- Shrinkage
  - b. MOST CHARACHERISTIC FEATURE : Chromatin condensation
  - c. 2nd MOST " " : Cell- Membrane intact.
  - d. ∴ NO INFLAMMATION
  - e.



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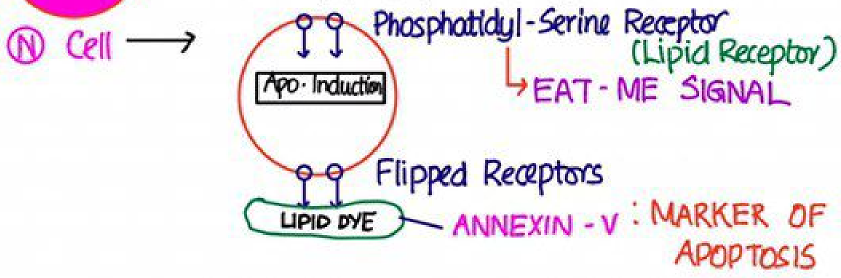

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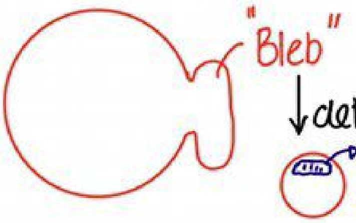
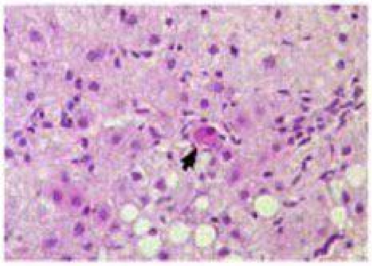
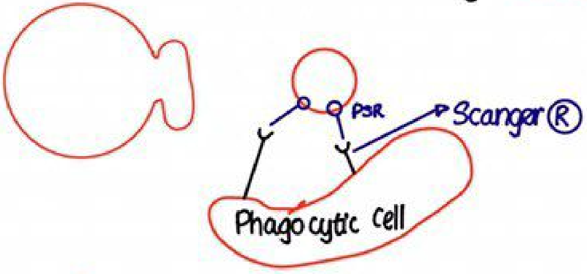




APOPTOTIC BODIES
Cell membrane bound structures with tightly arranged organelles with or without nuclear fragments. Examples are Councilman Bodies in viral hepatitis

Apoptotic Bodies :
Membrane bound structure with organelle & they may or may not have nuclear remenents.
→ Eg: Councilman bodies

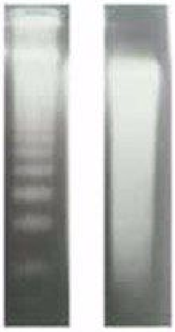
h.



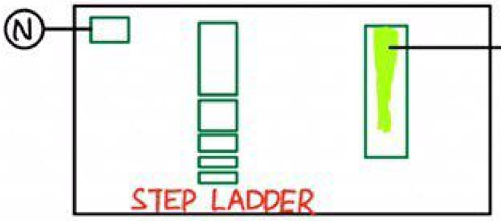
END OUTCOME = Phagocytosis

- BIOCHEMISTRY : pro- Caspase (pro-C)
↓ activation
Caspase → Endo nuclease activation
↓
Chromatin condensation

Function : Nu DNA damage as specific fragments
INTER NUCLEOSOMAL DNA DAMAGE
Size of fragments : 180-200 Base pairs
Can be observed Agarose Gel Electrophoresis



AGAROSE GEL ELECTROPHORESIS
A) Step ladder pattern of apoptosis. It is due to endonuclease induced internucleosomal damage
B) Diffuse smearing pattern seen in necrosis.



Smearing Pattern
⇓
seen in
Necrosis

Step ladder seen in
i) Apoptosis : Charachteristic
ii) Necrosis

MECHANISM OF APOPTOSIS

2 events

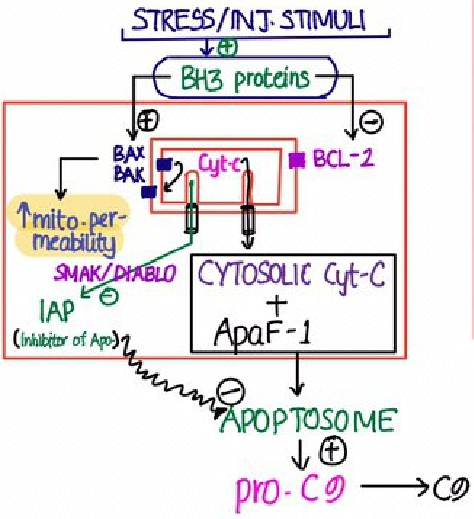
INITIATION ⊕ ⟹ EXECUTIONAL

INITIATION
- Pathways
  - INTRINSIC PATHWAY ↓⊕ C-9
  - EXTRINSIC PATHWAY ↓⊕ C-8 (In lower animal), C-10 (In Humans)

EXECUTIONAL
↓
$C_{7,6,3}$ activation
↓⊕
Endonuclease
↓
Chromatin condensation
(≐ Apoptosis)

INTRINSIC PATHWAY

- aka Mitochondrial pathway as mitochondria is the M. important organelle
- It's a major pathway



PROTO-ONCOGENE

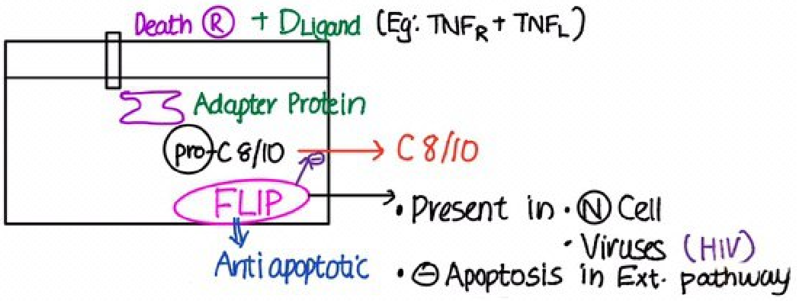
a. PRO-APOPTOTIC
- BAX
- BAK
- BCL-X_S
- BH_3 only proteins family (on cell surface)
  * STRESS-SENSORS
    - Bim
    - Bad
    - Bid
    - PUMA
    - NOXA

b. ANTI-APOPTIC
- BCL-2
- BCL-X_L
- MCL-1

SMAK/DIABLO : Inhibits IAP
∴ They are pro-apoptic

EXTRINSIC PATHWAY

- aka Death Receptor mediated pathway
  - i) TNF - Receptor : MOST WELL-DEFINED
  - ii) FAS / CD95



FLIP
- Present in
  - Ⓝ Cell
  - Viruses (HIV)
- ⊖ Apoptosis in Ext. pathway

FLIP : · Anti-apoptotic protein present in · Normal cell
· Viruses (HIV)
· ⊖ apoptosis at extrinsic pathway by inhibiting the formation of C8/10

Hallmark of Apoptosis activation : Caspase activation

Hallmark of neuronal apoptosis activation: AIF (Apoptosis Inducing Factor)
↳ No caspaces

Clinicopathological Co-relation

⇒ Misfolding of proteins ⟶ ↑↑ Misfolded protein : Feature of neurological disorders
~~↓⊕~~
Caspase
↓
Apoptosis

i. Alzheimer ds
ii. Parkinsons ds
iii. Huntigton ds

NECROPTOSIS

- Programmed cell death without caspase activation
- Necrosis + Apoptosis
  - Necrosis ↓ Morphology
  - Apoptosis ↓ Programmed cell death
- Mechanism :

TNF_R + TNF
↓ Recruits
RIP-1 + RIP-3 (Receptor Interacting Protein)
↓

↓ without caspase
Mitochondrial Stress
↓
FR production
↓
i. Cell swelling
ii. CM damage
iii. Inflammation

} MORPHOLOGY OF NECROSIS = NECROPTOSIS
∴ considered as variants of Necrosis

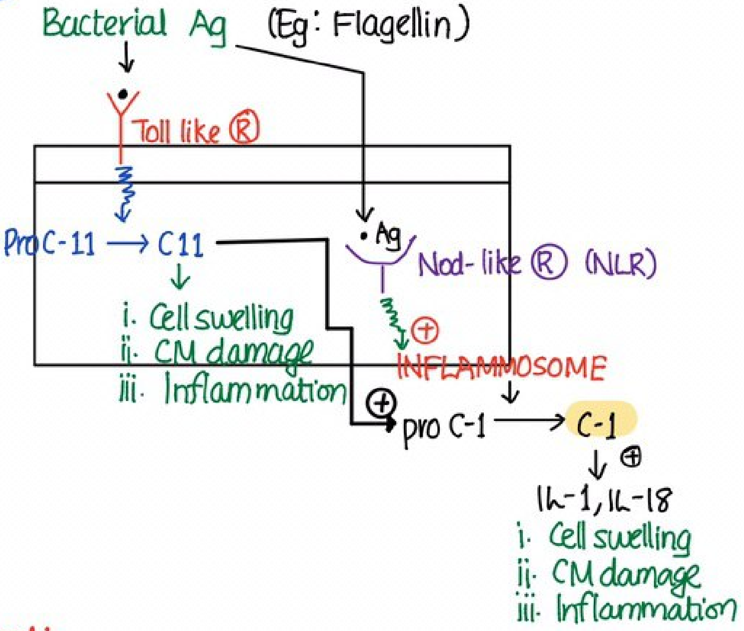
↓ ⊕
C-8
↓
Apoptosis (Extrinsic)

- NECROPTOSIS is both Physiologic & Pathologic
  - Physiologic ↓ Eg : Mammalian Bone growth plate formation
  - Pathologic ↓
    i. Neurological disorder
    ii. Pancreatitis

PYROPTOSIS

- Pyrogen induced Apoptosis
  ↳ IL-1

- Variant of necrosis
- Mechanism :



Chronic Injurious Stimuli

↓ leads to

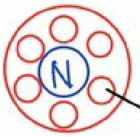
Intracellular accumulations

i. Ⓝ Substances
- Lipid (MC)
- Glycogen
- Proteins
- Pigments
  - i. Lipofuschin
  - ii. Hemosiderin
  - iii. Melanin

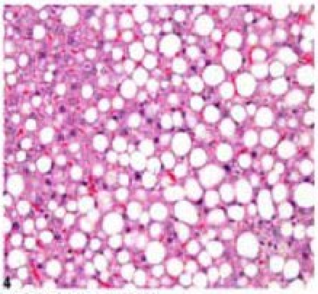
ii. Abnormal Substances
Coal / Silica

iii. Calcification

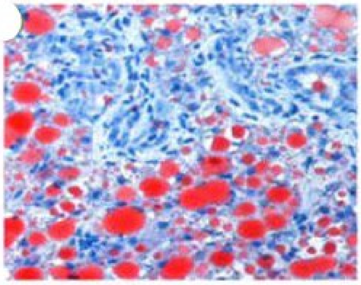
LIPID :
- MC intracellular accumulation
- aka STEATOSIS (↑ Lipid deposit c̄ in cell)
- it can be Triglycerides (TG) : $\underbrace{\text{MC Lipid accumulation}}_{\text{Alcoholic / NAFLD / Hepatitis / Viral}}$
  Cholesterol
  C. Esterases
  Phospholipid



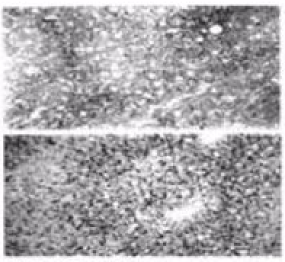
Clear Vacoules : SPECIAL STAIN
i. Oil-Red-O-stain : Lipid will be Red → Best stain in FROZEN/CRYO SECTION
ii. Sudan Black-B : Lipid will be black



INTRACELLULAR FAT.
It will appear as clear space with eccentric nuclei displaced y fat within cells.

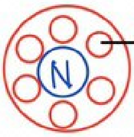


OIL RED O STAIN
Fat Globules will appear Orange Red. Best for lipid detection *on frozen section.



SUDAN BLACK STAIN
showing Fat Globules as black deposit

GLYCOGEN :



SPECIAL STAIN
i. PAS +ve
ii. Best's Carmine stain } GLYCOGEN IN RED COLOUR

PROTEINS : ↑ protein synthesis
↓
misfolding of proteins
↓
Ⓝ Responce : UPR (Unfolding Pr. Response)
↓

Stress on ER
↓
Synthesis of chaperons
(Req. for proper folding of proteins)

↓ ⊕
Autophagy
(Programmed cell death)
↑ prt. Misf ⟶ ⊕ IC protein degradation
↓
Ubiquitin + Protein (target)
↓
Taken in to Autophagosome & combine with Lysosome
↓
Degradation of proteins

↓ ⊕
Caspases
↓
Apoptosis

failure of Unfolding Protein Response
↓
Misfolding protein disorder

Autophagy /Ubiquitin Proteasome Degradation pathway is a/w
i. Atrophy
ii. Inflammation (TB)
Atgs-5 gene controls : Ⓝ phagocyte function of macrophage
↓
Deletion
↓
↑ TB
iii. Cancers (dsyregulated)
iv. Mitochondrial inheritance

PIGMENT ACCUMULATION

N. Pigment
i. Lipofuschin
ii. Hemosiderin
iii. Melanin

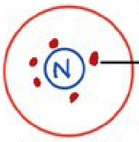
Abnormal Pigment
i. Lipofuschin
ii. Hemosiderin
iii. Melanin

PIGMENTS

- BROWN
  - Lipofuschin
    - * Oil-Red-O
    - * Sudan Black B
  - Hemosiderin
    - * PEARL'S PRUSSIAN BLUE STAIN
- BLACK
  - Melanin * in · Skin (Normal
    - · Melanoma
    - * Special stain : Fontana Masson

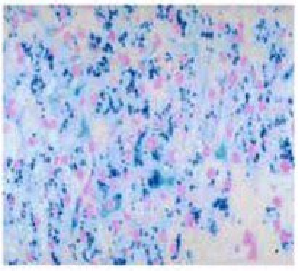
LIPOFUSCHIN : · aka Ageing pigments

FR → damage CM



- · Made up of Phospholipid + Proteins (dominants)
- · Seen in : * cancer cachexia
  - * severe malnutrition
  - * ageing

∴ it's aka TELL-TALE SIGN OF FR-INJURY
aka WEAR & TEAR Pigment


PERL'S PRUSSIAN BLUE STAINING
Showing Ferric Iron Deposits as Bright Blue.

CALCIFICATION

- Seen in ↑ alkaline pH of tissue
- Starts in mitochondria
  except for Kidney
  ↳ Starts in Basement Memb.
- Pathological Calcification

DYSTROPHIC
- * Tissue - damage
- * Ca^{2+} level : Normal

Eg : i. TB Lymph node
ii. Rheumatic heart disease
Valve damage
iii. Monckeberg Medial Calcific Sclerosis
iv. Psammoma Bodie
Seen in · Meningoma
· Mestholioma
· Papillary RCC
Thyroid

METASTATIC
- * Normal tissue
- * High Ca^{2+}
- * MCC :
  1° HYPER PARATHYROIDISM
  ⇓
  MCC : Parathyroid adenoma
- * Other causes
  i. Rena Failure (2° Hyper Para.)
  ii. Excessive Vit A & D synthesis
- * MC Site : Lung (Alveoli)
  Gastric mucosa
  Systemic artery

Least common : PARATHYROID

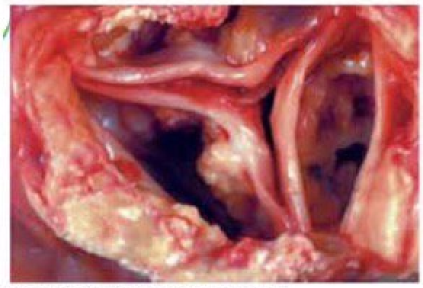
MIE : Basophilic Amorphous material (H&E)

↓ confirmation

MC & BEST : i) Von-Kossa stain : Black

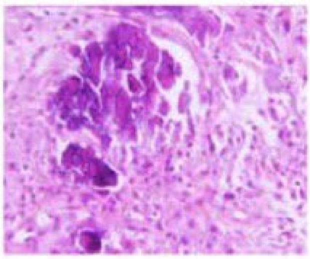
ii) Alizarin-Red : Red colour

Retinoic acids
↓ ⊕
Osteoclast
(modified macrophage)
↓
Bone-eating
↓
↑↑ Ca^{2+}



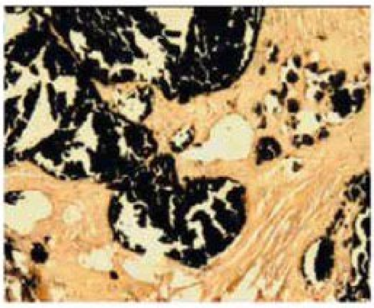
DYSTROPHIC CALCIFICATION

Dystrophic calcification of damaged valve in RHD.



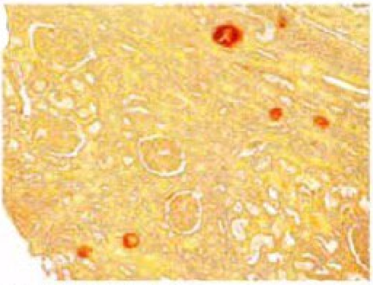
CALCIUM DEPOSITS (HEMATOXYLIN AND EOSIN STAIN)

calcium will be basophilic (blue) amorphous deposits.



VON KOSSA BLACK STAIN

showing calcium as black deposit.



ALIZARIN RED STAIN

showing calcium as red deposit.

AGEING

1. Progressive accumulation of sublethal inj. stimuli
↓
FR production : MOST WIDELY ACCEPTED HYPOTHESIS
↓
Ageing

2. Increased collagen deposition or Increase cross-linking of collagen
↓
Ageing

- Most effective method to prolong life span : Calorie-Restriction
↓ ⊕/induction
SIRUTUIN
↓
M.O.A
↖ ⊕/induce
Small amount of Red-wine

i. ↓ FR injury
ii. ↑ proper pr. folding
iii. ↓ apoptosis
iv. ↑ insulin sensitivity → ↑ Glucose metabolism
v. ↓ overall metabolism

- Changes in ageing : i. ↑ cell damage
  ii. ↑ mitochondrial damage
  iii ↓ glucose metabolism
  iv. DNA damage
  v. Telomere shortening

TELOMERE : - Short stretches of DNA @ the end of chromosome
- Function : i. Ensure complete replication of chromosome
  ii. Prevent fusion & degradation of chromosome
- Progressive cell division
  ↓
  Telomere shortening
  ↓
  Fusion/degradation of chromosome
  ↓
  Ageing
- **WERNER SYNDROME** v/s **WERMER SYNDROME**
  * Premature ageing d/t defect in DNA Helicase
    ↓
    Required for repair & Replication defective
  * MEN-I endocrine disoder

INFLAMMATION

Both protective & damaging
↓ Infections
↓ Autoimmune disease

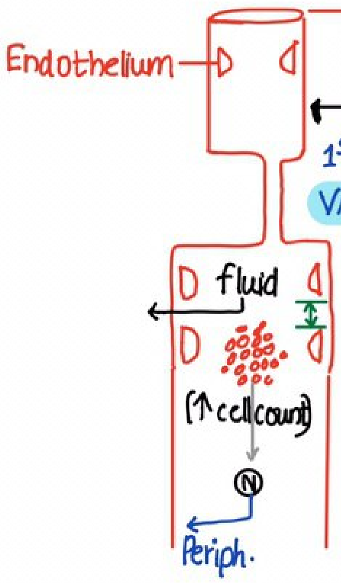
INFLAMMATIONS

ACUTE
- * Shorter duration (minute - hours)
- * Neutrophils : dominant
- * more clinical symptoms

CHRONIC
- * longer (days)
- * macrophages, Lymphocytes
- * milder symptoms

ACUTE INFLAMMATION

VASCULAR EVENTS



1st Responce / Earliest
VASOCONSTRICTION

2nd Event :
VASODIALATION

3rd Event :
↑ Vascular permeability : HALLMARK OF ACUTE INFLAMMATION

4th Event :
↑ viscocity → Stasis

Vascular Permeability : Mechanisms

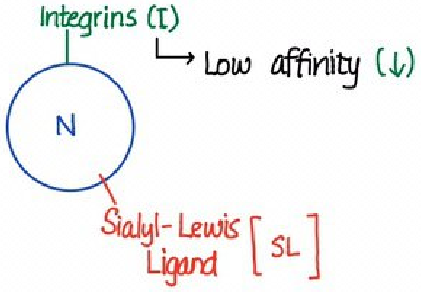
i. Endothelial Gap formation : Most important mechanism
- Occurs at the level of venules
  Except Lungs [Lungs by capillaries]
- It's immediate & transient responce

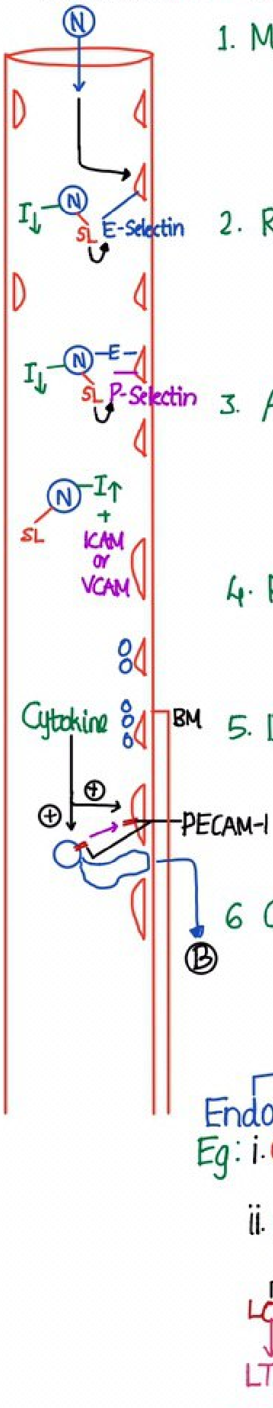
ii. Endothelial damage
a) Direct Endothelial Damage
- Will be immediate prolong responce

b) Mild Endothelial Damage
-Eg : Suburns
-Delayed & Prolonged

iii. Leuckocyte mediated damage
Delayed & Prolonged responce

CELLULAR EVENTS





1. Margination :
Transient attachment of Neutrophils to Endothelium via SL + E-Selectin

2. Rolling
via P-selectin
Transient attachment & detachment of Neutrophil

3. Adhesion
Strong attachment of neutrophil to endothelium via
$I_{(\uparrow / \text{High affinity})}$ + ICAM or VCAM

4. Pavementing
Overlaying of Neutrophil on Endothelial lining

5. Diapedesis : In Lungs at capillaries
Transmigration of leuckocyte via Endothelial Gap
Most important adhesion molecule in this step ∴ PECAM-1/CD31

6 Chemotaxis
Unidirectional movement towards chemotactic stimuli

- Endogenous
  Eg: i. Complement
  $C_{5a} > C_{3a} > C_{4a}$
  ii. Arachidonic acid metabolites
  - LOX → LTB_4
  - COX → $PGD_{2\alpha}$, $PGF_{2\alpha}$
- Exogenous
  Eg: Microbial Ag

7. Phagocytosis

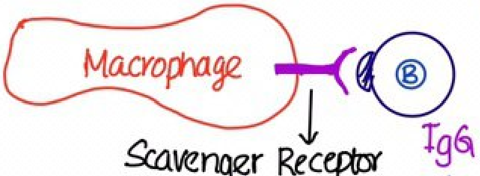
PHAGOCYTOSIS

- i. Neutrophil
  ii. Monocyte / Macrophage
  iii. Eosinophil [weak] → Parasite

STEPS OF PHAGOCYTOSIS

i. Recognition & attachment

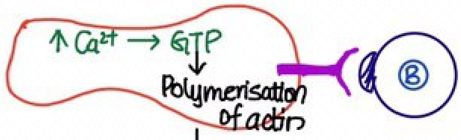
* Help in recognition
* Enhances phagocytosis
Eg: Antibody IgG > IgM
Complement C_{3b}



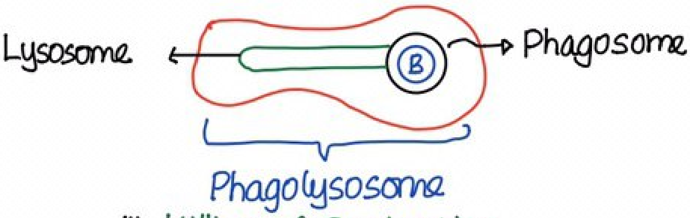
Scavenger Receptor
↓
Eg $FC\gamma_{IIIR}$

IgG
↓
F_c fragment / C_{3b}

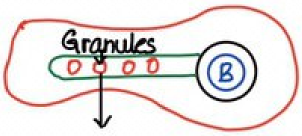
ii. Engulfment



↓
Contraction of cytoplasm
↓
Pseudopod formation (foot like processes)



iii. Killing & Destruction



Rupture = called as Respiratory burst
↓
NAPH - oxidase / Respiratory Burst oxidase / Phagocyte oxidase [controlled by PHOX gene]
↓
Produce Free radicals → Kills bacteria

After killing
↓
Acid-Hydrolases in Lysosome
degrades bacilli

PHAGOCYTIC KILLING

O2-dependent
* Most effective method
* With NADPH Oxidase

$O_2 \xrightarrow{} O_2^{\cdot}$
(Superoxide)
↓ Superoxide dismutase
H_2O_2 FR (weak)
↓ MPO Cl^-
HOCl¯ (Most effective)
(Hypochlorite)

* H_2O_2-MPO-Halide system

O2-independent
* involvement of
  i. Lactofferin
  ii. Lysozyme
  iii. Major Basic Protein
  ↳ in eosinophil

Clinicopathological Co-relation

Chronic Granulomatous disease (CGD)

- Defect : Respiratory burst
  ∵ of mutations in
  PHOX Gene

Membranous
(MC)
* X-linked recessive
* Genes :
  Gp91 PHOX gene mutation

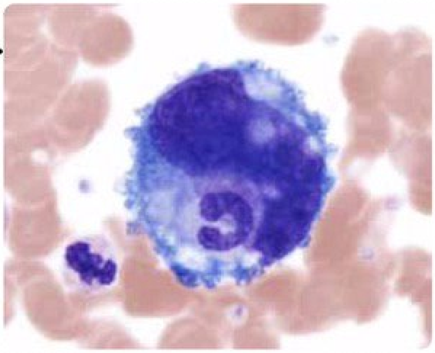
Cytoplasmic
* Autosomal recessive
* Genes :
  p47 & p67 PHOX gene mutation

- ∴ Recurrent infection with Catalase +ve
  Eg: Candida & Staphylococci
  ↓
  ∵ this will degrade H_2O_2
  ∴ halide will not be formed.

- Granuloma formation
- 1° immuno deficiency

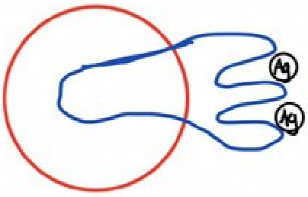
EMPERIPOLESIS

- Active penetration of one cell into another without changing morphology or physiology



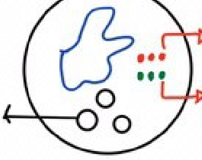
Eg: i. Megakaryocytic Emperipolesis : in Myelodysplastic Syndrome
ii. Leuckocytic Emperipolesis : in CML
iii. Autoimmune Hepatitis

NEUTROPHILIC EXTRACELLUR TRAP



Pathogenesis :

Exposure to microbial Ag to Neutrophil
↓ ⊕
LPS / IL-8
↓ ⊕
Neutrophil



Lysosomal granules ←
* MPO
* Lactofferin

→ NADPH Oxidase
→ PAD-4 (Protein Arginine Deimidase)

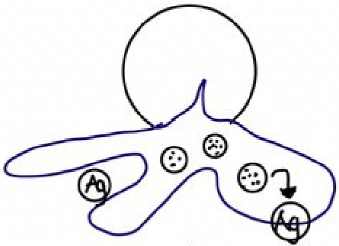
↓

- NADPH Oxidase
- PAD-4

Rupture of Lysosome Granules
↓
- MPO
- Lactofferin
- Lysozyme

Citrullinisation of Histones
⇓
Decondensation of Chromatin
↓
Histone degradation products

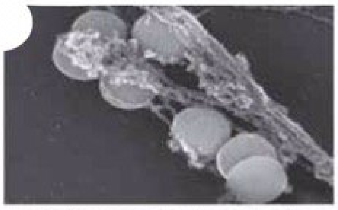
↓



Microbial antigen destroyed

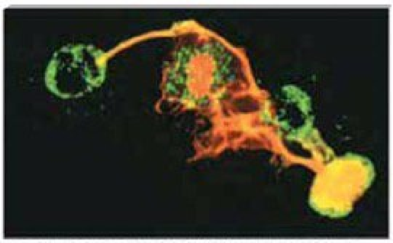
function :
i. Antimicrobial (Protective) (Most important)
ii. Nuclear chromatin Exposed
↓
∴ Anti-Nuclear Ab (ANA) formed
↓
∴ a/w Auto immunity
iii. Deep vein thrombosis

# also known as Beneficial Suicide



NEUTROPHIL EXTRACELLULAR TRAPS (NETS)

Electron microscopy shows Networks of extracellular fibers, primarily composed of DNA from neutrophils, whi pathogens for killing them extracellularly and minin damage to host cells.



NEUTROPHIL EXTRACELLULAR TRAPS (NETS)

Neutrophils with nuclei stained red and cytoplasm green.) Networks of extracellular fibers, primarily composed of DNA from neutrophils, which bind pathogens for killing them extracellularly and minimizing damage to host cells. In this process nuclei will be lost and causing death of neutrophil also (beneficial suicide)

ADHESION MOLECULE

Selectin
* required for cell to cell interaction
* 3 types
  P Selectin : Platelet
  E Selectin : Endothelium
  L Selectin : Leuckocyte
  ↓
  CD62

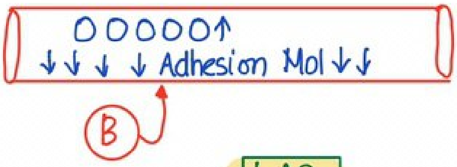
Integrin
* Cell to cell & Cell to matrix
* function
  i. Adhesion
  ii. Arrest
  iii. Transmigration
* Rolling is not a function : by P-Selectin

Ig Molecule
*PECAM-I/CD31

Mucin like protein
* in ECM
* Heparan Sulphate

Clinicopathological Co-relation

- Defective adhesion molecule
  ↓
  Leuckocyte adhesion defect disorder (LAD)
- AR disorder
- a/w Primary immunodeficiency



Neutrophilia / Leukocytosis without Pus formation

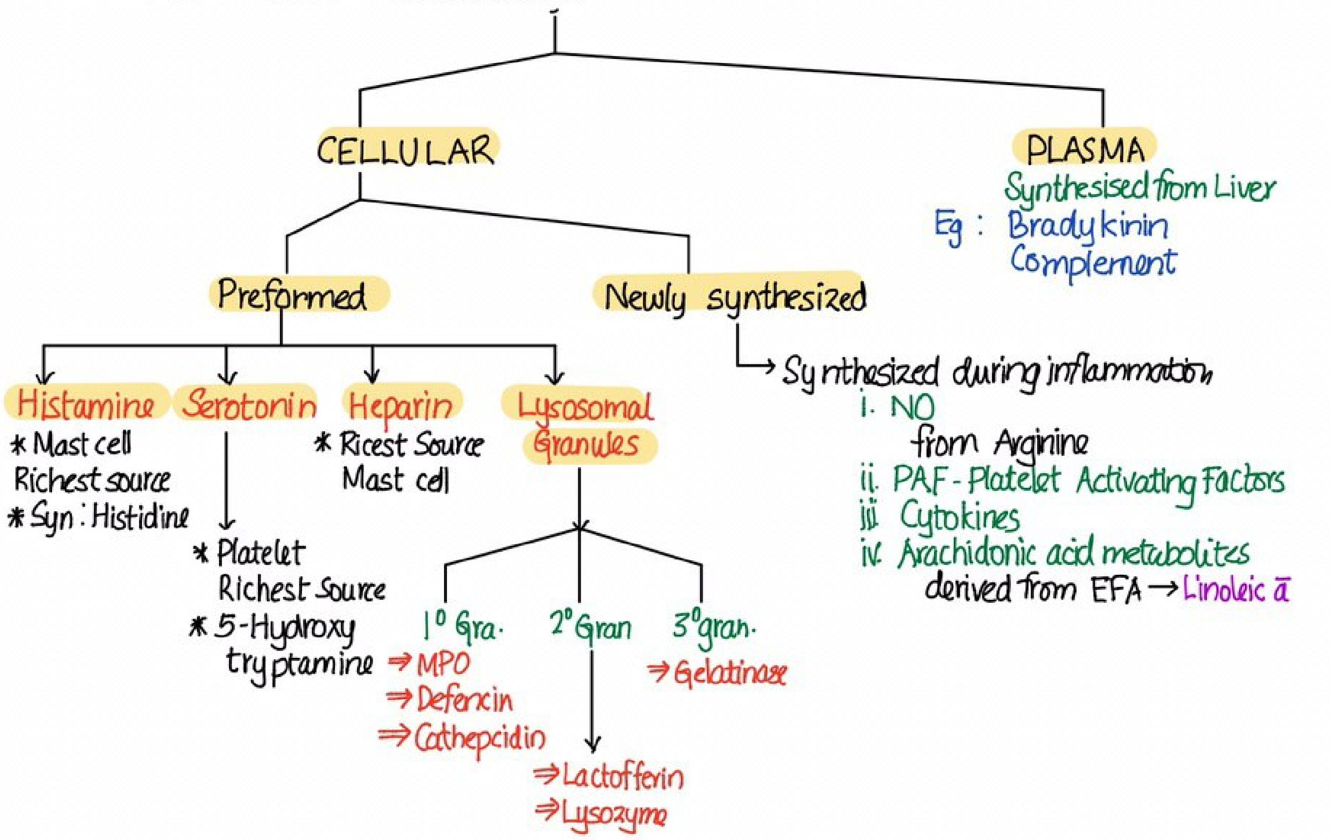
LAD

I
- β_2 chain of β_2 Integrin
- C/f : • Delayed seperation of umblical cord stem [> 30 days of birth]

II
- Sialyl Lewis defective
- C/f : Mental Retradation a/w Bombay blood Group

III
- Mutation in FERMT-3 gene
  ↓
  No activation of $\beta_1, \beta_2, \beta_3$ integrin
- C/f : Bleeding like platelet disorder k/a Glanzmann's Thrombasthenia

INFLAMMATORY MEDIATORS



Histamine / Serotonin / PAF / Bradykinin

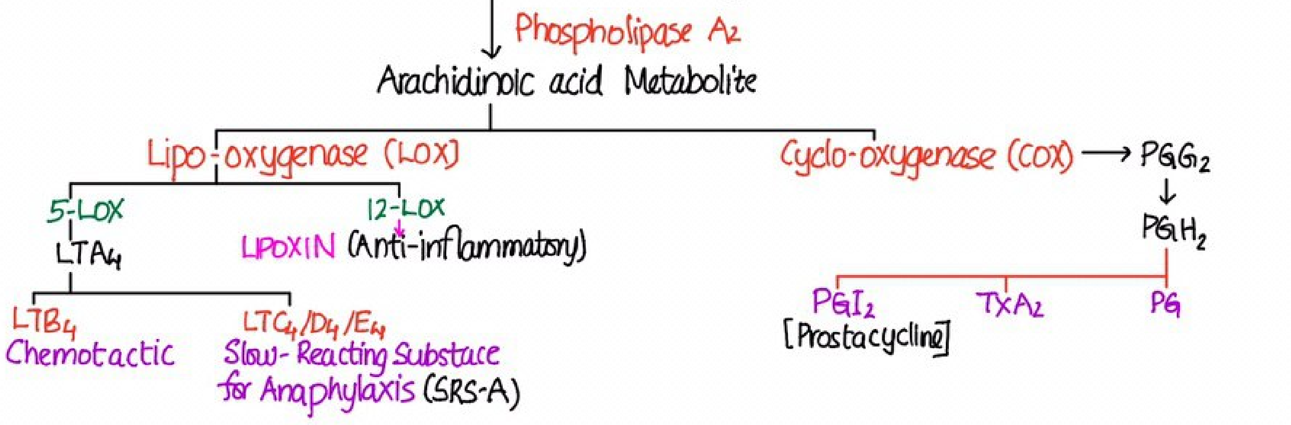
* Vasoconstriction

Most important function : PAIN
" " " in acute inflammation : ↑ vascular permea.

- Functions : i. vasodilation
ii. ↑ vascular permeability
iii. Smooth muscle constriction
(Bronchoconstriction)

Arachidinoic acid Metabolites

- Derived from Phospholipid containing EFA Linoleic acid


Phospholipase A_2
Arachidinoic acid Metabolite
Lipo-oxygenase (LOX)
5-LOX
LTA_4
LTB_4
Chemotactic
$LTC_4/D_4/E_4$
Slow- Reacting Substace for Anaphylaxis (SRS-A)
12-LOX
LIPOXIN (Anti-inflammatory)
Cyclo-oxygenase (COX) → PGG_2
PGH_2
PGI_2
[Prostacycline]
TXA_2
PG

LIPOXIN : * Endogenous Negative Regulator of Neutrophilic Chemotax.
* inhibit Neutrophil Chemotaxis
* activation of Macrophages for Phagocytosis of Neutrophil

Prostacycline : * Richest source endothelium
* Anti- platelet aggregator
* vasodialator

TXA_2 : * Richest source : Platelet
* Platelet aggregation
* Vaso constriction

$PGE_{2\alpha}$: * a/w Fever & Pain

$PGF_{2\alpha}$, $PGD_{2\alpha}$ } * a/w Neutrophilic chemotaxis

Cytokines

- These are soluble proteins
- Sources : Synthesized by — Hematopoeitic / Non-Hematopoeitic
- They are highly specific

Eg: IL-2 : NK cells & Lymphocyte growth
IL-4 : Mast cell
IL-5 : Eosinophil
IL-6 : Plasmacells
IL-8 : Neutrophil Chemotaxis , NET

- CHEMOKINES :
  - Small molecular wt cytokines which are associated with chemotaxis.

C-X-C / α Chemokine	C-C / β-Chemokine	C / γ Chemo.	$C-X_3-C$
* IL-8 : Chemotaxis of Neut.	* Chemotaxis of all cells except Neutrophil Eotaxin : Eosinophil Rantes : Lymphocytes	* LYMPHOTACTIN Lymphotaxis Chemokine	* FRACTALKINE for interaction of Monocytes with Platelet.

MOST IMPORTANT CYTOKINE

i. Fever / Pyrogen : IL-1
Others : IL-6, TNF-α, IFNα, Cillary Neurotropic factor, $PGE_{2\alpha}$
ii. Acute inflammation
iii. Septic shock
iv. Cancer Cachexia } TNF-α

v. Angiogenesis : Vascular Endothelial Growth Factor (VEGF)
vi. Fibrosis : TGF-β
vii. Granuloma formation : IFN-γ
viii. Acute Phase Responce Protein [APR] :
- Most important Cytokine : IL-6
  Others : IL-1 / TNF-α
- They are altered during inflammation

Increased	Decreased
+ve APR	-ve APR
Eg: S.ferritin CRP Fibrinogen	Eg : Albumin Transferrin

- APR can be ↑ in acute & chronic inflammation

ix. Morphogenic & Mitogenic : Bone Morphogenetic Protein / BMP
↓ This is a member of TGF-β

Morphogenic ↓ Organogenesis, Embryogenesis
Mitogenic ↓ Cell proliferation, Cell differenciation

x. Anti-inflammatory Cytokine :
- Any cytokine which is antagonist of IL-1 or TNF-α
- Role :
  - Inhibit proliferation & differenciation of autoreactive or autoimmune cells
  - A/W wound healing & Repair
- Members : IL-4 / 6 / 10 / 13 / TGF-β
  * Both anti & pro inf. function

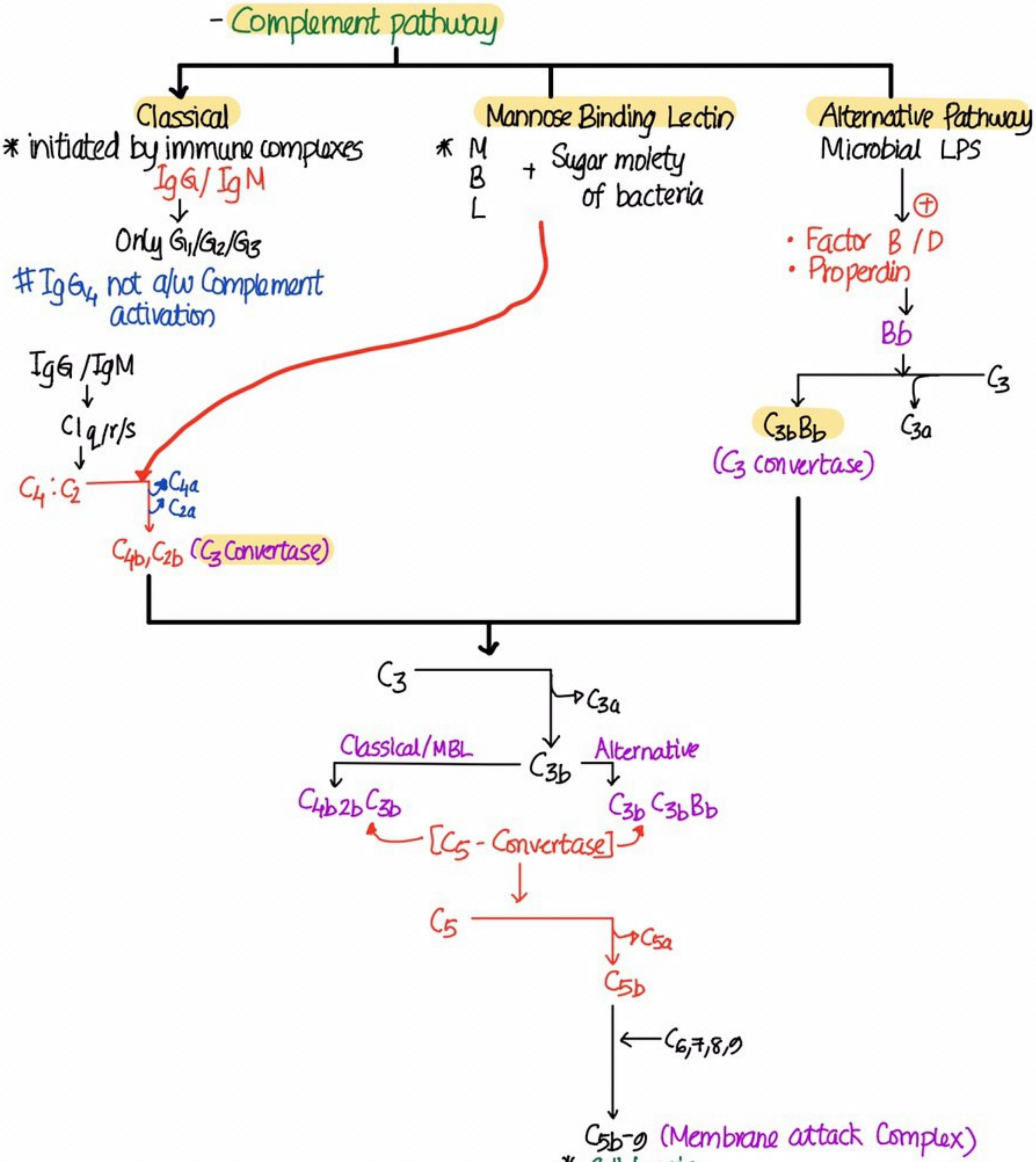
Plasma Mediators

i. Bradykinin : formed by Factor XII [Haegeman Factor)

$$\begin{tikzcd} & \text{XII} \arrow[d] & \\ & \text{XII}_a \arrow[d] & \\ \text{PRE-KALLIKREIN} \arrow[rr] & & \text{KALLIKREIN} \arrow[d] \\ & \text{Kininogen} \arrow[r] & \text{Kinin (Bradykinin)} \end{tikzcd}$$

ii. Complement
- Liver proteins
- a/w Both adaptive & innate immunity
  ↓
  Complements & their products are a/w Regulation & Development of B & T Cell

- Complement pathway



- * Cell Lysis
- * M.O.A: by punching hole in to cell membrane
- * C9 is most important as it's having Perforin like activity

defective MAC
↓
* Recurrent infection by Capsulated organism
↓
Recurrent Neisserial infection

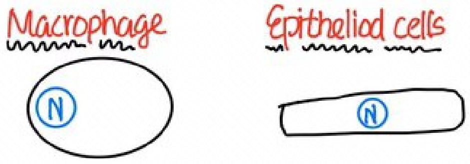
CHRONIC INFLAMMATION

STEPS:

Ⅰ Mono-nuclear cell infiltaraction
Lymphocytes
Macrophages: Dominanent
⇓
Cytokines
↓
Ⅱ Tissue destruction: HALLMARK
↓
Ⅲ Repair/Wound healing

Granulomatous Inflammation

- Pattern of chronic inflammation
- Mechanism: TB antigen
↓ ⊕
Macrophage
↓
IFN-γ
↓ ⊕
CD_4 TH1 Cell
↓
IFN-γ Release
↓ Lymphocyte proliferation & Differentiation
↓ Convert to Macrophage to Epitheliod cell

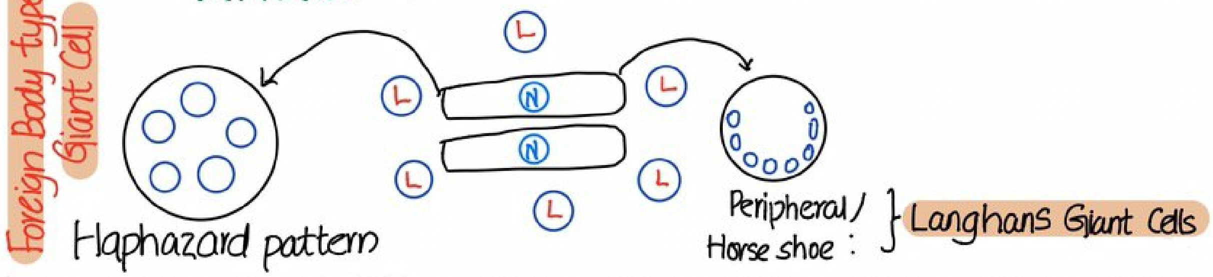


Macrophage:
* Round - Oval nucleus
* Eccenteric nucleus
* foamy cytoplasm

Epitheliod cells:
* Elongated Slipper shaped
* Central Nucleus

# Epithelium	Epitheliod
• Cell Supported by BM Eg: Brunner gland cells	• Cluster of cell ʒout BM Eg: Pancreatic islet cell Testicular Leydig cell Testicular Lutein cell

- Definition :


Foreign Body type of Giant Cell
Haphazard pattern
L
N
Peripheral / Horse shoe : } Langhans Giant Cells

Granuloma is epitheliod cells on center surrounded by collar Lymphocytes accomponied by Giant Cells.

Types of Granuloma

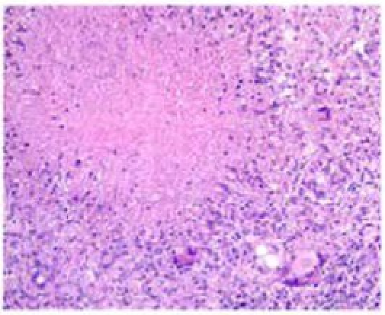
Caseating
Eg: TB
Histoplasmosis
Coccidiodomycosis

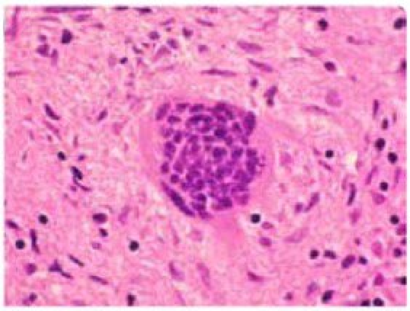
Non-caseating
Eg: TB
Sarcoidosis
Hodgkins Lymphoma
Leprosy : Tuberculoid

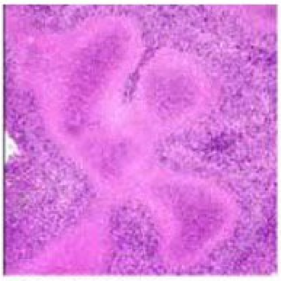
Special
i. Naked granuloma
In Sarcoidosis
* No Lymphocytic/ Scanty Lymphocytic infiltarate

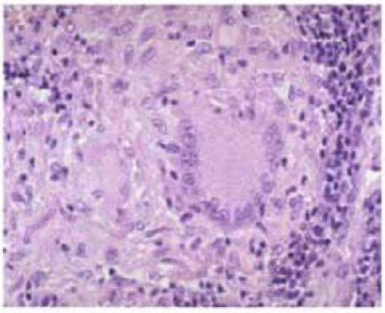
ii. Stellate granuloma
* Neutrophilic granuloma
* M/E: Star shaped Necrosis
* Seen in Cat-scratch disease

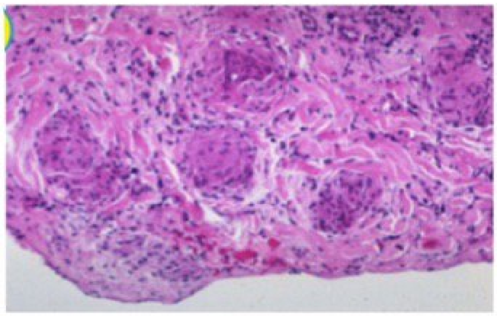
iii. Durck's Granuloma
* in cerebral malaria by Plasmodium falciparum

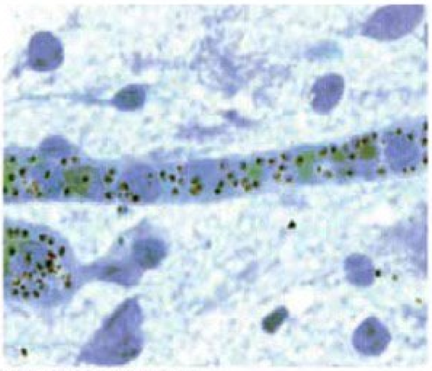

GRANULOMA (SCANNER VIEW)
Tuberculous granuloma with caseous necrosis and Giant cells.


FOREIGN BODY TYPE GIANT CELLS
Haphazard Nuclear arrangement


STELLATE GRANULOMA
cat scratch disease showing "stellate abscesses" characterized by foci of necrosis surrounded by granulomatous inflammation with giant cells.


LANGHANS GIANT CELLS
Peripheral arrangement or horseshoe shape arrangement of nuclei


NAKED GRANULOMA (SARCOIDOSIS)
Naked' granulomas are composed of epithelioid histiocytes and multinucleated giant cells with no or only sparse infiltrate of mononuclear cells at the periphery.


DURCK GRANULOMA
Seen in cerebral malaria. Blood vessels packed with rings of P. falciparum.

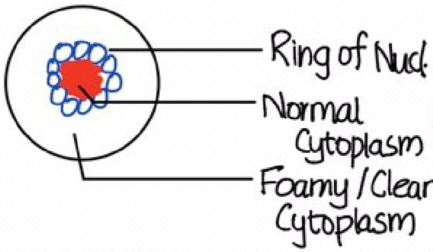
Giant Cell

Physiological

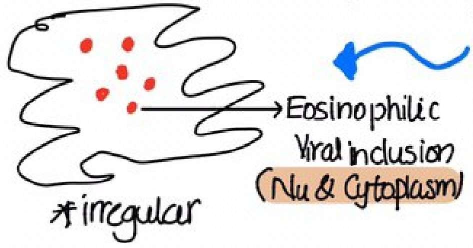
i. Megakaryocytes
ii. Osteoclast

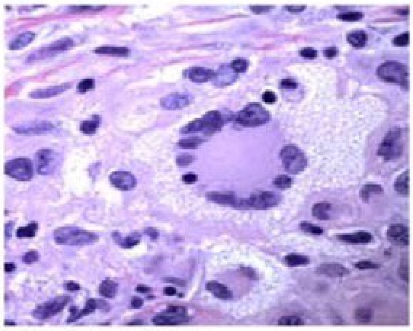
Pathological

i. Aschoff Giant Cell
in Rheumatic H.D
ii. Reed-Sternberg cells
in Hodgkin Lymphoma
iii. Touton's giant cell
in Xanthoma

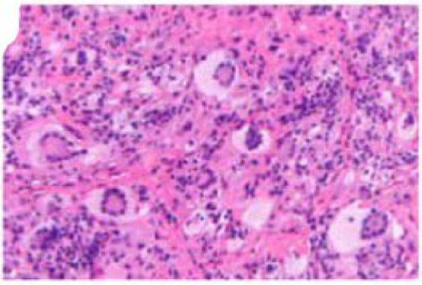


iv. Warthin finkeldey G.C
In measles
Atypical pneumonia known as
HECHT'S PNEUMONIA





TOUTON GIANT CELL
Multinucleated giant cells containing a ring of nuclei surrounding a central homogeneous cytoplasm, while foamy cytoplasm surrounds the nuclei. The cytoplasm surrounded by the nuclei has been described as both amphophilic and eosinophilic, while the cytoplasm near the periphery of the cell is pale and foamy in appearance



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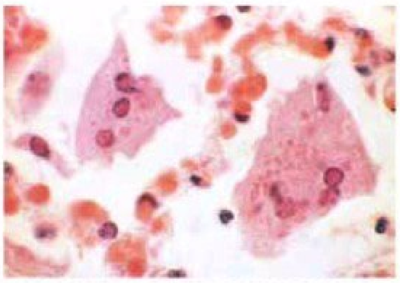


WARTHIN FINKELDEY GIANT CELLS
Multinucleated giant cells with eosinophilic nuclear and cytoplasmic viral inclusion bodies.

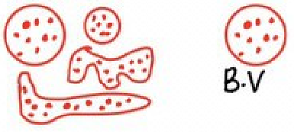
WOUND HEALING

- 3 Steps
  1. Complete Resolution
     - in minor injury
  2. Regeneration
     - complete restoration of lost tissue by proliferation of parenchymal cells in adjacent areas.
     - Parenchymal cells
       - i. Labile Cells
         - * Continous division throughout life
           Eg: BM Cells
           Skin epithelial cells
       - ii Stable cells
         - * Non-dividing cell but stimuli → Growth
           Eg: Liver, Kidney cells
       - iii. Permenent cells
         - * Non dividing cells
           Eg: Cardiac & Neurons
  3. Repair
     - Lost tissue replaced by fibrocollagenous tissue
     - Consists of 2 events
       - i. Formation of granulation tissue
       - ii. Wound Contraction

Granulation Tissue

Hallmark of wound healing

- Components
  - i. Proliferating blood vessels (leacky)
    ↓
    Variable shape & size B.V



  - ii. Proliferating fibroblasts
    These haphazard arrangement of fibers
  - iii. Non-specific mononuclear cell infiltarate

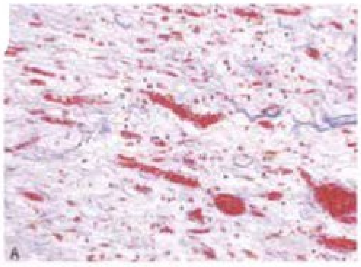
Types of collagen

bONE, skin : Type I collagen
* max. tensile strength
* in scar also ⊕

carTWOlage : Type II Collagen
Reticular : Type III Collagen
↑ In granulation tissue
Basement Mem : Type IV Collagen

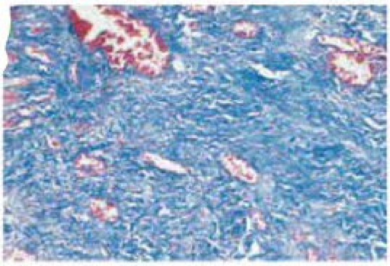
Masson's Trichome stain

Stain fibers blue colour



GRANULATION TISSUE

consisting of proliferating capillaries filled with RBCs and accompanied by fibroblasts producing collagen.



GRANULATION TISSUE (MASSON'S TRICHROME STAIN)

consisting of proliferating capillaries filled with RBCs and accompanied by fibroblasts producing collagen (blue colors).

Wound Contraction

- By myofibroblast
  - → Mesenchymal origin
  - → On EM: Special type of fibroblast with smooth muscle like contractility
- It's because of tissue Re-modelling

⇓

Granulation Tissue (Type - III) —Zinc / Matrix Metallo Proteinase (MMP)→ Scar formation (Type - I Collagen)

CUTANEOUS WOUND HEALING

Primary Cutaneous Wound Healing	Secondary Cut. Wound Healing
* Surgical incision ↓ wound healing is with clean opposed edges	* inj → loss of tissue ⇓ Wound Healing with Gap formation
	* wound contraction more prominent

Day-wise changes in cut. wound. healing

Lifespan : 7-10 days

DAY - 1 : Earliest cell to appear ⇒ Platelets ≫ Neutrophil
Cell which appear first by Chemotaxis ⇒ Neutrophil
↓
Life span : i) Peripheral Blood: 6hrs
ii) Tissue : 1-4 days

DAY - 3 : Neutrophil will be replaced by Macrophages
Early granulation tissue formation

DAY - 5 : Maximum granulation tissue
Epidermal thickness is recovered.
i.e Stratum corneum is seen

DAY - 14 : Max collagen deposition

DAY - 28 (1month) : Completion of scarring

	Cutaneous W.H	Myocardial infarction W.H
	* More earlier	* Delayed
Earliest Granu. tissue	Day-3	* 7-10days
Maximum Granul. tissue	Day-5	* 10-14 days
Completion of Scarring	1month	* 2months

Wound Strength : - Directly proportional to Collagen Deposition [Cross-linking]

- Vit C : Hydroxylation of Lysine & Proline

$$\text{Tropo collagen} \longrightarrow \text{Collagen}$$

∴ Strength of wound increased.

- Start increasing by day 5-7 days i.e 10% of original strength
- 100% strength of original strength : Never achieved
- Maximum strength : 70-80% at the end of 3^{rd} month

In foetal cutaneous wound healing : NO SCARRING
∵ i. No expression of Osteopontin gene (Req. for Fibrosis)
ii. Presence of Nonfibrogenic TGF-β
iii. Lack of involvement of CD_4 T_{H2} cells

for more notes,join our telegram channel, "latest neet pg notes 2020" or join via link " t.me/latestpgnotes"

Macrophages
↓
Activated macrophages

Classically activated / M_1

- * activation by IFN-γ
- * secretion : IL-2, IL-12
- * function : Microbial killing
  Pathological inflammation

Alternatively activated / M2

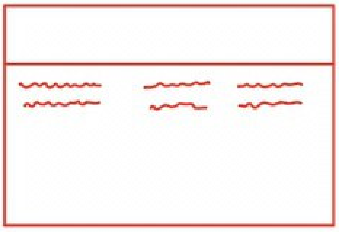
- * activated by : $CD_4 T_{H2}$ cells
  ↓ Release
  IL-4, 5, 6
  ↓ ⊕
  M_2
- * Secretions : IL-10, TGF-β
- * function :
  - i. Wound Healing & Repair
  - ii. Prevent auto-immunity

SCAR

HYPERTROPHIC SCAR

- * Scarring is limitted to original wound
- * may regress spontaneously
- * no genetic association

* M/E

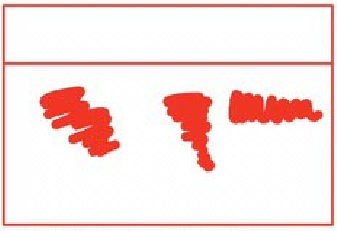


* thin collagen
parrellel arrangement to skin surface

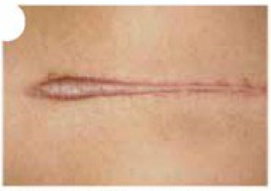
Keloid

- * Scar tissue is beyond the boundaries of original wound.
- * no spontaneous regression
- * Genetic association
  Seen in african origin
  MC Site : STERNUM

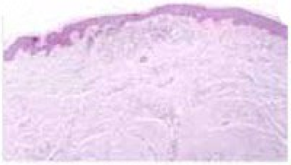
*M/E



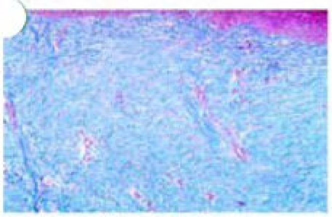
* Disorganised dense / thick Collagen



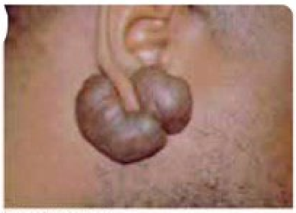
HYPERTROPHIC SCAR (GROSS)
Scar tissue do not grow beyond the boundaries of the original wound and may regress spontaneously.



HYPERTROPHIC SCAR (LM)
Scar tissue with thin collagen bundles that is oriented parallel to skin surface.



MASSON'S TRICHROME STAIN
howing hypertrophic scar.



KELOIDS (GROSS)
Scar Tissue extends beyond the borders of the original wound and it does not usually regress spontaneously.

GENETIC DISORDERS

Genetics : Study of genes

CODING
(=Exons)
· It's only 1.5% of human genome

NON-CODING
(=Introns)
· consist of 98.5% of human genome

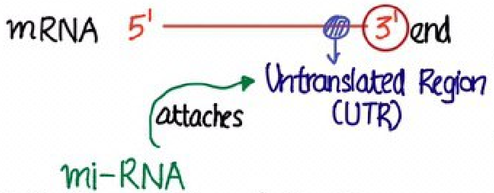
Telomeres & Centromeres

Non Coding RNA
i. micro-RNA
ii. LNC-RNA
iii. pi-RNA
MC Non coding RNA in human genome

Jumping Genes / Transposons
↓
* Continously moving within our human genome
* constitute 33.3% of human genome
* function : Chromatin organisation

MICRO-RNA (mi-RNA)

- 5% of human genome is miRNA
- function : Gene silencing RNA
  ⇓
  Post-transcriptional Gene silencing



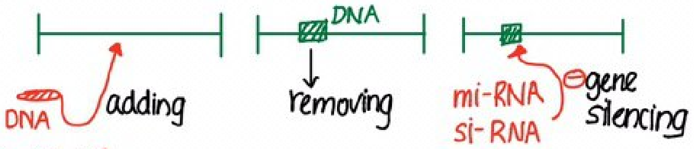
- mi-RNA consists of 21-30 Oligonucleotides
  ↓
  ∴ called as micro-RNA

- Eg of Gene silencing :

mi-RNA ⊖→ Tu-gene ⇒ No tumor
mi-RNA ⊖→ Tu.suppressor gene ⇒ Tumor

- Exogenous mi-RNA is called as Small interfering RNA (SiRNA)
- Genetic Engineering (3 technology)

Gene knocked in | Gene knocked Out | Gene knocked down



LONG NON-CODING RNAs (LNC-RNA)

- consist of 200-500 nucleotides.
- Function :

a) Gene silencing
↓
Eg : Barr-Body formation d/t inactivation of XIST gene

b) Gene activation
↓
Eg : Stabilise teritiary structure of protein
↓
Regulating chromatin organisation & gene activity

GENETIC DISORDERS

SINGLE GENE DISORDERS

a) Classical Inheritance
(Mendelian inheritance)
- i. AR (Autosomal Recessive)
  MC inborn-error of metabolism
- ii. AD (Autosomal Dominant)
  MC pattern : in 65% cases
- iii. X-linked Recessive
- iv. X-linked dominant

b) Un-classic inheritance
- i. Trinucleotide Repeat mutation
- ii. Mitochondrial inheritance
- iii. Genomic Imprinting
- iv. Gonadal mosaicism.

MULTIPLE GENE DISORDERS

aka Multifactorial inheritance
(or) Complex Polygenic inheritance
↓
involvement of >2 mutant gene
+
Environmental Factors
↓
Eg: i. Diabetes Mellitus
- ii. Cleft lip
  Cleft palate
- iii. Congenital Heart dis.
- iv. HTN
- v. CAD
- vi. Gout

CHROMOSOMAL DISORDERS

a) Numerical disorders
- i. Euploidy
- ii. Aneuploid

b) Structural disorders
- i. Deletion
- ii. Translocation
- iii. Ring chromosome
- iv. Isochromosome
- v. Inversion

1 gene

1 maternal allele
1 paternal allele.

AUTOSOMAL DOMINANT	AUTOSOMAL RECESSIVE
* Heterozygous : considered as Diseased	* Heterozygous : considered as Carrier
* Homozygous : die in utero	* Homozygous : disease

AUTOSOMAL DOMINANT DISORDERS

I. variable expressivity : single gene with different expression in different individual

Eg NF-1 gene
→ macules (1st individual)
→ Iris (2nd individual)
→ spine (3rd individual)

II. Pleotropism : 1 gene is responsible for different expression in same individual

Eg: SCA gene ↓ mutant gene
⇒ Hemolytic A
⇒ Lungs
⇒ Spleen
⇒ Bone

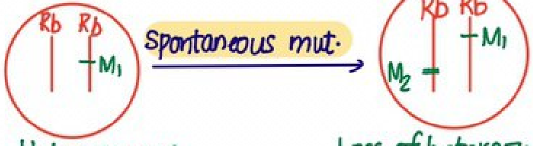
III. Incomplete penetrance : presence of mutant gene but phenotypically normal.

Eg: RB gene (Chr. 13q 14)
↳ • AD
• Heterozygous : Normal

KNUDSON'S TWO HIT HYPOTHESIS

at the Time of Birth

Later on acquire another mutation



Heterozygous
(Normal)

Loss of heterozygosity

IV. Dominant - Negative effect.
mutant gene is affecting normal genes & products

Eg : seen in those genes encoding multimeric proteins i.e fibrillin (or) Collagen
↓
Triple Helix (Glycine-X-P)
Glycine ↓ Mutant
X-P ↓ Normal
Abnormal Collagen ⇐

# Fibrin mutation	Collagen mut.
↓	↓
# marfan syndrome	# Ehler Danlos Synd. (EDS) # osteogenesis imperfecta.

Eg of dominant negative effect.

EHLER-DANLOS SYNDROME

- Heterogenous disorder consiting of
  TYPE - I to VIII
  becoz multiple collagen are effected
- Overall AD is most common pattern
- Collagen - 3 is most commonly effected
- Type-3 EDS : Most common
  Type-7 EDS : Least common
- C/f :
  - i. Hyper extensibility of Joints + Skin
    ↓
    Rubher-like elasticity
    aka Rubher-man Syndrome
  - ii. Abnormal Scar tissue (Thin cigarette paper like scarring)
  - iii. Spontaneous Rupture Colon + Arteries
    EDS Type IV (aka Vascular EDS)
    ⇓
    Worst prognosis (d/t sudden death)

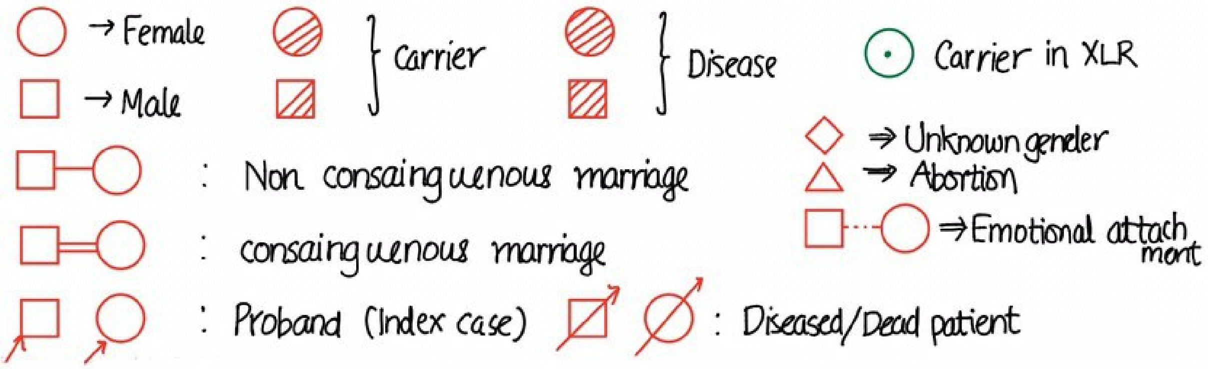
OSTEOGENESIS IMPERFECTA

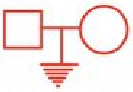
- pediatric
- Fracture of Bone + Blue Sclera
- Type-1 Collagen is effected

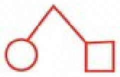
MARFAN SYNDROME.

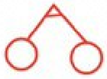
- AD ; Ch 15q
  ↓
  I. fibrillin 1gene mutation (MC)
  II. TGF-β mutation
- fibrillin : Stabilise elastin.
  Elastin get deposited over fibrillin
  ↓
  ∴ Elastin contain tissue effected
  Eg: Aorta
  Lens
  Heart
- C/f : Triad
  - a) Skeletal Deformality (M. Charact)
    - i. Tall stature
    - ii. Thin & long fingers
      ↓
      Arachnodactly
      (Spider like)
    - iii. Hyper extensibility of joint.
  - b) Eye
    - i. Lens dislocation
    - ii. Retinal detachment
  - c) Cardiac
    - i. Cystic Medial Necrosis
      ↓
      - Aneurysm &
      - Regurgitation of aorta
      - Mitral valve Prolapse
      - Dissection of Aorta. } MCC of Death
- Diagnosis: Revised GHENT'S Criteria
  - i. Family history
  - ii. Fibrillin - 1 gene mutation
  - iii. Charachteristic Signs & Symptoms

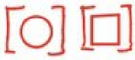
PEDIGREE SYMBOLS




: Sign of infer tility

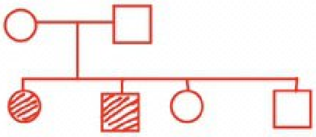

: Dizygotic Twin


: Monozygotic twin


→ Adoption

APPROACH FOR PEDIGREE ANALYSIS

1. Rule out Unclassic inheritance : i. Gonadal Mosaism
   ii. Mitochondrial inheritance
2. Rule out XLR & XLD
3. Rule out AD & AR


GONADAL MOSAICISM

- Both parents : Ⓝ
- Variable No·of Kids effected } Unclassic Inheritance

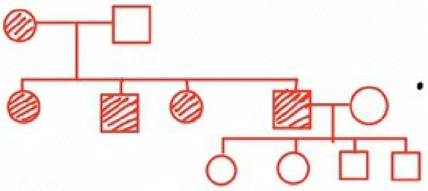
⇒ Mutation in gamates in parents

⇓

∴ Gonadal mosaicism → variant of AD disorder

No·of mutant Gamates ∝ No·of affected Kids

- Eg : Achondroplasia (AD disorder)
  Osteogenesis imperfecta


MITOCHONDRIAL INHERITENCE

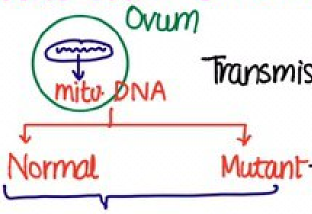
- female was effected
  ↓
  all her children were effected
- But her son's children are not effected

} Unclassical Inheritance

⇓

∴ Mitochondrial inheritance
aka Maternal inheritance
↓
bcoz ovum is rich in mitochondria

Eg :
i. Leber's Hereditary Optic Neuropath (proto type)
ii. MELAS : Mitochondrial Encephalopathy Lactic Acidosis & Stroke like features : (MC)
iii. NARP : Neurogenic weakness Retinitis pigmentosa.



Mutant → if above threshold limit → Transmission to next generation

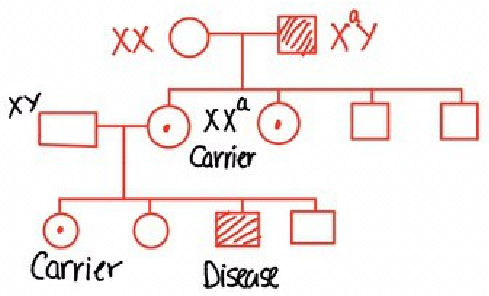
Heteroplasmy : Same organelle having both normal & mutant DNA

- Sperm mitochondrial DNA undergo selective degradatio
  by Ubiquitin - Proteosome degradation pathway

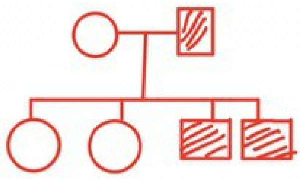
X LINKED RESESSIVE :

XX ↓ going to both son & daughter

X Y ↓ going to daughter only



- Only males are effected
- Females are carrier/Normal
- ↓ may be effected :
  - Turner Syndrome
  - Random X -inactivation
- Eg of XLR :
  - i. G6PD def. Anemias
  - ii. Hemophilia - A
  - iii. Fragile X Syndrome



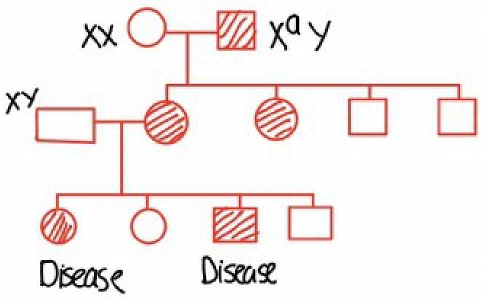
- Only males are affected
- Father to son transmission

⇓

Y-linked Disorders

Eg: Hypertrichosis (Hairy ear)

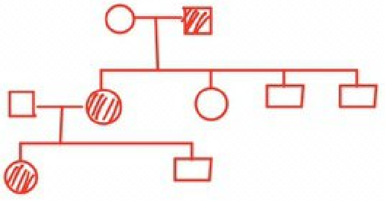
X-linked dominant



- From affected father only daughters will be effected
- Son are spared
- From the affected daughter
  - 50% daughter
  - 50% son

  will be effected

Eg: • Alport Syndrome (MC)

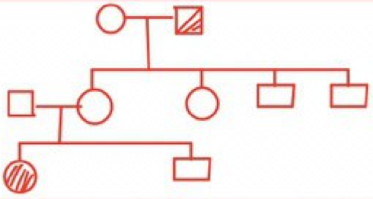


- No gender gender bias
- No skipping of generation

⇓

Autosomal dominant

Eg: Achondroplasia
Marfan Syndrome
NF-1 & 2

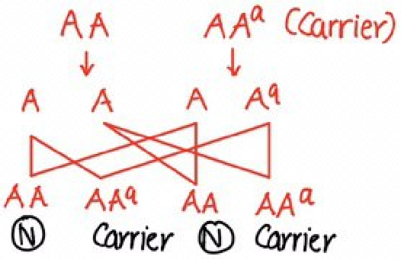


- No gender bias
- Skipping of generation present

⇓

Autosomal Recessive

AR



} 0% is effected

In an AR disorder One parent is normal & another is carrier. But one child is affected. Which mechanism?

AA × A(A^a)

↓

A^aA^a

Uniparental disomy: One parent is giving both chromosomes.

⇓

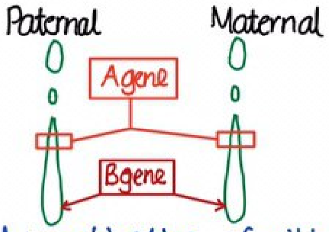
Rare phenomenon.

GENOMIC IMPRINTING

↓

Inactivation

- Normal phenomenon
- Every gene
  - Paternal allele
  - Maternal allele



- **Genomic imprinting**:
  - Differential inactivation of either maternal or paternal of alleles
  - Functional allele is inherited from one parent only

↓

involve certain genes in certain chromosome

- Mechanism of Genomic imprinting : Epigenetics

↓

defined as hereditary chemical modification of DNA or histones.

↓

Reduced expression of gene ⇐ { i. Methylation of DNA/Histones (MC)
ii. Deacetylation of Histones.

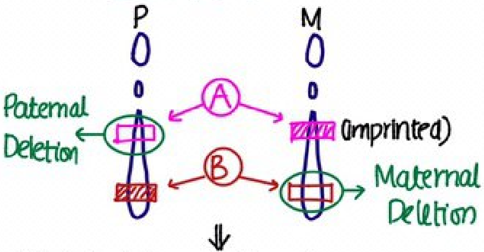
- Chr. 15q is a/w
  - Prader-Willi Syn. (PW)
  - Angelman Syndrome (AM)

Molecular mechanism :
i. Deletion (MC) (70%)
ii. Uniparental disomy (15-20% cases)
iii. Abnormal Genomic imprinting.

MECHANISM

- DELETION
- UNIPARENTAL DISOMY
- ABN. GENOMIC IMPRINTING

DELETION

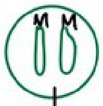


Maternal imprinting, Paternal deletion } ⇒ PW

Maternal deletion, Paternal imprinting } ⇒ AM

UNIPARENTAL DISOMY

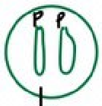
of Maternal



- Both are from mother
- No paternal

⇓ Pradder-Willi Syndrome

of Paternal



- Both are from father
- No mother

⇓ Angel Man Synd.

Clinical Features of PW

- Obesity (d/t ↑ GHRELLIN Hormone)
  - ↓ Oraxagenic Hormone i.e ↑ appetite
  - ↓ Secreted from antrum of stomach
- Mental Retradation
- Hypo gonadism

Clinical Features of AM:

- aka Happy Puppet syndrome
  - inappropriate laughter
  - Ataxic movement
- GHRELLIN : normal in AM.

# UNIPARENTAL DISOMY IS A/W

i. Prader-Willi Syndrome

ii. Angel man Syndrome

iii. Russel Silver syndrome

iv. Beck weidth-weidman Syndrome
a/w Wilm's Tumor- type-2

TRINUCLEOTIDE REPEAT MUTATION

- aka DYNAMIC MUTATION
- Normal Codons arranged in Triplet (Eg: CAG)
  - ↓ Repitition upto 6-55 times (Normal)
  - ~ 30 times (avg)
- When no. of Repeats 55-200 : These are called Premutation
  - ↓ pt will be like carrier
  - No symptoms

>200 repeats : Overt disease : Symptoms starts

NO. OF REPEATS ∝ SEVERITY OF DISORDER

↳ ↑ no. of repeats during Oogenesis & Spermatogenesis.

- ↑ in No of Repeats occurs
  - → **Oogenesis** : involve introns
    - Eg: i. Myotonic dystrophy (Chr. 19q)
    - ii. Fragile X - Syndrome
    - iii. Friedrich ataxia
  - → **Spermatogenesis** : involve exons
    - Eg i. Huntington's Chorea
    - ii. Spinocerebellar ataxia

HUNTINGTON DISEASE

- CAG Repetition
- AD ; on chromosome No: 4
- Age : 40-60 yrs

Consider Father with : 300 TNR
: onset 40yrs
↓
Spermatogenesis
↓
Son with : 600 TNR (↑ Severity)
: onset : 25yrs

} ANTICIPATION a/w TNR
i. ↑ Severity of disease
ii. Early onset
in next generation

FRAGILE -X SYNDROME

- These are X-linked Recessive
- Males > Female
- Chromosome with fragile site
  ↓ Folate def medium
  will get prominent

- C/f :
  - i. Mental Retardation
    - one of the common cause
    - Male with IQ 20-60
  - ii. Most charachteristic : Macro orchidism (large testis)
  - iii. Large Face, Ear, Mandible
    - # Nose is normal or small

CHROMOSOMES

- Study of Chromosome : Karyotyping

Karyotic Idiogram

i) Chromose arranged in pair
ii) Arranged in ↓ order of length
∴ XY chromosome is placed at ends
Largest Chromosome : Chr : 1
Smallest Chromosome : Chr : 21

- Samples used for karyotyping
  - i. Amniotic fluid contain
    - · shedding of epithelium of Skin, GIT, Urogenital tract
  - ii. Chrionic villia Biopsy
  - iii. Peripheral Blood Lymphocytes only (bcoz it can proliferate in vitro)
    - # monocytes are not used
  - iv. Fetal Tumor samples
    - MC Fetal Tumor : Teratoma

for more notes join our telegram channel, "latest neet pg notes 2020" or join via link "t.me/latestpgnotes"

v. Cordosentesis : Ultra sound guided Blood sampling of umblical cord Blood vessel.

- Fixatives of choice for Karyotyping

- Fixative of choice : $\underbrace{\text{Methanol + Glacial Acetic Acid}}_{\text{CARNOY'S FLUID}}$

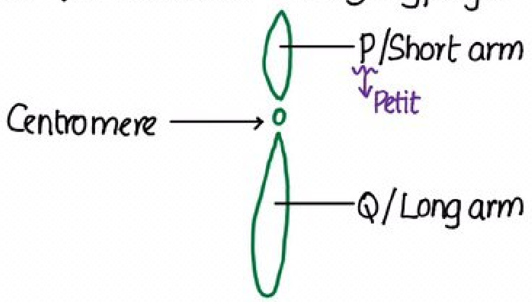
- For histopathology : 10% of Formalin
- For Electron microscopy : Glutaraldehyde
- For Cytological Smear / PAP Smear : 05% of Ethanol
- For Testicular Biopsy : Best : BOUIN'S Fluid (Picric acid)
  Universal Fixative : 10% formalin.

BOUIN'S FLUID Useful for : Reticuloendothelial Cell
Hematopoeitic stem cell

- Collection of sample → Fixation → Cell proliferation
↓ Colchicine alkaloid
Metaphase arrest
(Routine Karyotype)
Draw back :
only 400-800 bands / Karyotype
↓
Resolution is low

To Increase Resolution
↓
PROPHASE - ARREST
(1500 bands / K)

MC & Best for stain for Karyotyping : Giemsa - stain (G-Banding)



P/Short arm $\xrightarrow[\text{into}]{\text{divided}}$ Regions $\xrightarrow[\text{into}]{\text{divided}}$ Bands
↓
Sub Bands

Eg:
Chr 13 q 14.2
No. Arm Region Band
Sub band.

On the basis of centromere : 4 types

1. METACENTRIC
   P = q
2. SUB-METACENTRIC Eg : X Chromosome
   P < q
3. ACROCENTRIC Eg : Y chromosomes
   P <<< q Chr. 13, 14, 15, 21, 22
   - centromere at extreme end
   - a/w Robertsonian Translocation
     (a/w Pathogenesis of Down Syndrome trisomy 21)

- Robertsonian Translocation is a/w
  t (21: 21)
  t (21: 22)
  t (21: 13/14/15)

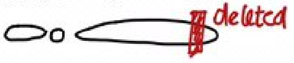
4.

TELOCENTRIC not seen in human beings

CHROMOSOMAL DISORDERS

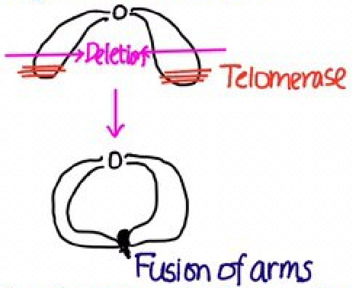
STRUCTURAL DISORDERS

i. Deletion of Chromosome



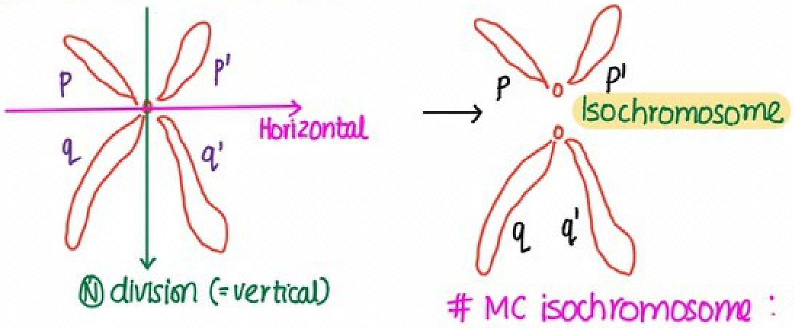
a/w Cancers & Leukemia

ii. Ring chromosome



a/w Sarcomas & Turner Syndrome.

iii. Isochromosome formation.



MC isochromosome : iXq

MC isochromosome in human cancer : i17q → a/w Medulloblastoma

i12p a/w → Seminoma/ Germ cell Tumor

NUMERICAL DISORDERS

MC chromosomal abnormality
Trisomy 16: die in utero

MC chromosomal abnormality in live birth : Trisomy 21

Limitations of Karyotyping
i. Can't detect complex translocation
Eg: t(0: 22)
ii. can't detect amplifications
Eg: N-MYC amplification in neuroblastoma
iii. Micro deletion can't detected.
MC Microdeletion
Digeogrge Synd. (22q)

to overcome these limitations
FISH > PCR

FISH : BEST FOR DETECTION OF KNOWN GENE LOCI
LIMITATION : Can't detect smaller gene mutation (Eg: Point mutation)

PCR : BEST FOR DETECTION OF POINT MUTATIONS
Limitation : Can't detect LARGE GENE MUTATION

Multiplex Ligation Probe Amplification (MLPA)

- Basic principle : Principle of FISH + PCR
- Can overcome both limitation
- Use. : Duchenne's muscular dystrophy
  Cystic fibrosis

NUMERICAL ABNORMALITY

I. Deletion : Eg: Cri-du-chat syndrome (d/t Chr 5p−)
- Mental Retradation
- Developmental delay
- Cat-like cry (mewing)

II. Autosomal Cytogenetic Disorder : Eg: Trisomy 21 (= Down syndrome)
Trisomy 13 (= Patau syndrome)
Trisomy 18 (= Edward syndrome)

III Cytogenetic disorder a/w Sex Chromosome : Eg: Klinfilter Syndrome
Turner Syndrome

PATAU-SYNDROME

- Trisomy 13
- Features :
  - i. Appearance : Microcephaly (Small head)
    Microopthalmia (Small Eye)
    Low set ears
  - ii. Mental Retradation
  - iii. Heart : Congenital Heart disease
  - iv. Gross : Holo prosencephaly
    (No Rt & Lt cerebral hemisphere)
  - v. Rocker Bottom Feat
- a/w advanced maternal age
- Survive : upto 1yr

EDWARD SYNDROME

- Trisomy 18
- Features
  - i. Prominent occiput
  - ii. Microcephaly
  - iii. Cleft lip & Cleft palate
  - iv. Hand : Clenched fist with overlapping finger
  - v. Rocker Bottom feet ·
    (MC in Edward syndrome)
    Trisomy 18 > 13 MC
- a/w advanced maternal age
- Survive : upto 1yr

DOWN SYNDROME

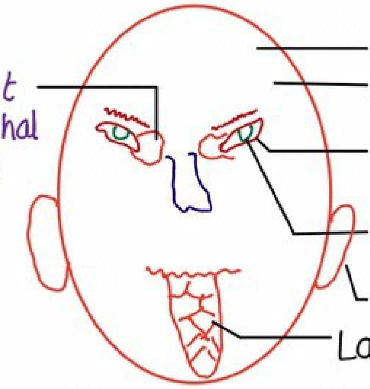
- Trisomy 21
- Pathogenesis :

Meiotic Non disjunction
(MC - 95%)
- ✱ can be maternal or paternal
  - ↓ a/w Maternal Age
  - ↓ Not a/w Pat. age ·
- ✱ Extra chromosome : Maternal
- ✱ occurs during MEIOSIS - I except for Edward Synd.

Robertsonian Translocation
(~4%)
- ✱ not a/w Maternal age
- ✱ MC familial
  - t(21:14) (MC)
  - t(21:21) (Chance is 100%)
  - t(21:22/13/14/15)
- ✱ if any parent is have these translocation go for Adoption

Mosaicism
(~1%)
- ✱ d/t mitotic non disjunction
- ✱ not a/w maternal age.
- ✱ same individual normal & abnormal chromosome (46/47)

- Clinical Features



Prominent Epicanthal Folds

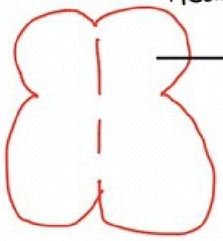
1. Flat Facial profile
2. Mental Retradation (MC genetic cause of M·R)
3. Oblique Palpebral Fissures } Mongaloid Slant

Brush field spots : whitish Spots on iris

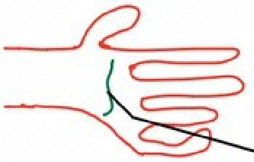
Low set Ears

Large protruding tounge with wrinkling
Scrotum like tongue

Heart



Congenital Heart disease :
MC : Endocardial Cushion defect > VSD > ASD



- Hands are
  - short
  - Broad
  - Fifth Finger curvature

Single Palmar Crease
(Simian Crease)

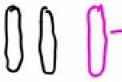
Otherfeatures :
- Duodenal atresia
- Mega colon
- Intestinal obstruction
- Hypotonia
- Foot : wide gap b/w First & second toe.

MC Leukemia in Down Syndrome : ALL > AML (MC AML : M7)
MC Leukemia in <3yrs old : AML (M7)

⊛ Down syndrome case surviving beyond 40yrs ⇒ universally effected by Alzheimer's Disease

Alzheimer's Disease is bcoz of Amyloid Precursor protein (APP) present on Chromosome 21

In Down syndrome :



→ Extra Chr. 21
↓
Extra APP protein
↓
Misfolding of protein

- Serum markers :

a) Triple marker
   i. AFP
   ii. Estriol
   iii. β-HCG

b) Quadraple marker
   i. AFP
   ii. Estriol
   iii. β-HCG
   iv. Inhibin-A

c) PAPP-A (Pregnancy associated plasma protein-A)

Increased in Down Syndrome
β- HCG
Inhibin A

Decreased in Down Syndrome
α- FP
Estriol
PAPP-A

markers used in **First trimester**
β-HCG
PAPP-A

, **Second Trimester**
Estriol
α-FP
Inhibin -A

SEX -CHROMOSOME DISORDER

1. TURNER- SYNDROME

- phenotypically Female
- Features :
  - Primary Amenorrhea (MCC -Turner)
- Karyotyping :
  - i. MC : 45 XO
  - ii. 46, iXq
  - iii. 46, r(X)
- Clinical Features :
  - i. short stature
  - ii. Webbing of neck
  - iii. Lymphadema of hands & extremity
  - iv. Broad chest & widely spaced nipples.
  - v. Short 4th metacarpal
  - vi. Streak ovary (small ovary) : Gross
    Atrophy of ovarian tissue : M/E
    ↓
    ∴ amennorrhea & infertility
  - vii. Insulin Resistance
    ∴ High Risk for Type-2 DM
  - viii. Pre cancerous & Pre leukemic
    ↓ Colon cancer ↓ AML

Preleukemic : Down syndrome
Klinfilter syndrome
Turner syndrome

  - ix. MC cardiac defect :
    Bicuspid Aortic valve > Coarctation of Aorta.

KLINEFELTER -SYNDROME

- Phenotypically Male
- MCC of Male hypogonadism
- Karyotyping :
  - i. 47 XXY (MC)
    XXXY

Klinefelter Syndrome } → X ≥ 2, Y ≥ 1

- Clinical Features
  - i. Mental retradation
    Each X Chromose ↓IQ by 15.
  - ii. Gynacomastia
    (d/t ↑ Estrogen)
  - iii. ↑ FSH, LH
  - iv. ↓ Testosterone
  - v. Testicular atrophy
  - vi. MC Tumor a/w Klinefelter
    ↓
    Breast Ca > Teratoma
    ↓
    Extra gonadal Teratoma
    MC : Mediastinum

RECENT ADVANCES IN GENETICS

I. GEEN (Genome Editing with Engineered Nucleases)

- Nucleases :
  - These are considered molecular scissors.
  - Require for Addition, Deletion or replacement of gene segment. in-vivo (in living organism)

- They will create target mutation called as Edits

# Nucleases : 4 types

i. Mega nucleases
ii. ZFN = Zin Finger Nuclease
iii. TALEN
iv. CRISP R/ Cas-9

# CRISPR is derived from Bacterial DNA Sequances

↓

Undergo transcription

↓

Transformation to gRNA (guide RNA)

consist of

a) Constant Region ↓ combine with Cas-9, derived from Prokaryote

b) Variable Region ↓ combine with target DNA Sequances.

⇒

⇓

Site specific DNA breaks are created

2 possibilities

- Removal of specific segment ↓ Repaired by Homologous DNA Recombination (HDR)
- Removal of non-specific segment ↓ Repaired by Non homologous End Joining (NHEJ) (most effective method)

Forms targeted mutation/edits

# now under trial for t/t : Huntington disease.

I. GENETIC POLYMORPHISM

- DNA sequance variation in any individual 99.5% similarity
  0.5% variation
- DNA variation b/w any 2 individual is Genetic polymorphism
  0.5% = 15 million base pairs
- Genes responsible for variation : Polymorphic Gene
- Uses of Polymorphic gene : Diagnosis of Genetic disorders with
  i. unknown mutant gene
  ii. multiple genes are associated.

properties.

- always closer to disease causing genes
- Transmitted from one generation to next generation stably called Linkage disequilibrium

- Types of polymorphic gene

Single Nucleotide Polymorphic Gene (SNP)
- MC Type
- When comparing of 2 individuals ↓ 1 nucleotide/1000 bp shows variation
- 1% of Exons are SNP
- considered as Marker loci of genetic disorders

Copy Number Variation (CCNV)
- variation of contigous DNA sequence of any 2 individual ranging from 1000- 1million BP
- >50% of exons
- Basis of phenotypic variation

Repeat Length Polymorphism
- d/t short repetitive DNA sequance variation
- 2 types
  - a) Microsatellite: 2-6 bp variation of repetitive seqance
  - b) Minisatelite: 15-70bp variation of repetitive sequance.

Polymorphic gene can be used for diagnosis of Genetic disorders.

- Single gene disorders
  - ↓ gene loci is well known
  - ↓ can use direct sequencing with
    - PCR
    - FISH
- Multiple Gene/Unknown mutant gene
  - ↓ Use marker loci (Polymorphic gene)
  - ↓ Indirect sequencing
    - Running in a family ↓ Linkage Analysis
    - Running in Large population ↓ Genome wide Analytical Studies

MOLECULAR DIAGNOSIS

I. Southern Blot : for DNA

II Northern Blot : for RNA

III Western Blot : for Protein

A) PCR : Polymerase Chain Reaction

- for short DNA segment
- BEST FOR DETECTION OF POINT MUTATION

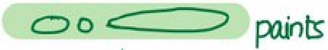
i) Sanger sequencing : for short DNA segment
ii) Pyro sequencing : for tumor samples contaminated by stromal cells
iii) Amplicon length analysis : for analysis of Length of DNA variation / Segment
Eg: TNR Mutation

iv) Real time PCR : Realtime detection & quantification can be done
Eg i. Philadelphia Chromosome in CML
ii. Infectious load in HIV (10C)

B) FISH

- for known gene loci
- Resolution : 200kb
- can detect · fast dividing cells Eg: Amplification
  Complex translocation
- 2 variants

i) Chromosomal Painting
Fluorochromosome (single colour)
Chr. 1



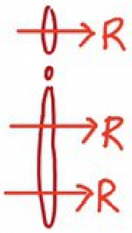
↓
Use: Detect entire human genome in same chromosome

ii) Multi colour fish / Spectral Karyotyping
>5 types of fluorochromes
+
Computer generated signals
Use : Detect entire human genome on all chromosome simultaneously
∴ aka Spectacular Karyotyping.

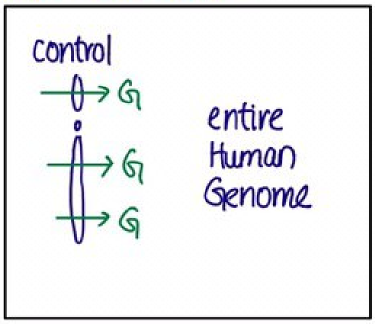
C) Micro-array Analysis

- aka Comparitive Genomic Hybridisation
  ↓
  Compare genome after hybridisation
- Use : to detect Unknown Gene locus
- On same chromosome how to detect Normal & Tumor gene simultaneously?
  take patient chromosome
  ↓
  Use 2 fluorochromes · Red
  · Green

Patient



Genomic Library



⇓
Perform Hybridisation on Array
↓
Fluorescent cameras capture colour
Computer screen

○ → Red :	Gain of Gene	Eg: Amplification (or) mutation
○ → Green :	Loss of gene	Eg: Deletion
○ → Yellow :	Normal areas	

* Uses of micro-array : i. Gene expression profiling

Eg : Ca. Breast

on the basis mRNA gene expression

- Estrogen Receptor Expression ↓ ER ⊕
- Progesterone-R expression ↓ PR ⊕
- Her2/Neu R Expression ↓ Her2/neu ⊕

ii. Molecular classification of cancer

Eg: Ca - Breast

for more notes,join our telegram channel, "latest neet pg notes 2020" or join via link " t.me/latestpgnotes"

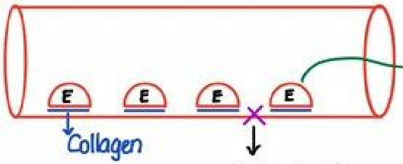
BLEEDING & COAGULATION DISORDER

Hemostasis	v/s	Thrombosis
* Normal Physiological process where blood is maintained in a fluid state within vessel. and inducing hemostatic plug at injured site		* Pathological process where inappropriate/excessive activation of hemostasis present * Clot/hemostatic plug in uninjured blood vessels (or) even after minor injury

Components of hemostasis / Thrombosis:

- i. Endothelium
- ii. Platelet
- iii. Coagulation pathway

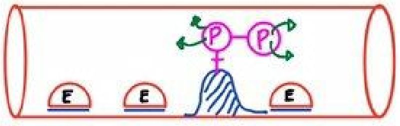
# Minor injury under normal condition
↓
Bleeding stops spontaneously



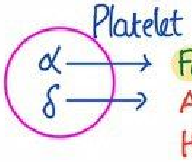
→ Smooth - Endothelial lining
↓
No clotting : Ⓝ BV

Minor cut
↓
Bleeding stops spontaneously
d/t REFLUX VASOCONSTRICTION
↓
d/t Endothelin

# Major cut



Major injury
↓
Sub-endothelial collagen exposed
↓
Platelet attaches
↓↓
Platelet + Platelet : weaker
(1° Hemostatic plug)



α → Factor V, VIII, Fibrinogen, TGF-β
δ → ADP, Ca^{2+} (Factor IV)
Histamine, Serotonin

} ⊕ Coagulation Pathway
↓
Formation of Fibrin
(2° Hemostatic plug)

ENDOTHELIUM

When it get injured release

↓

PRO-COAGULANT
- * vWF

ANTI-COAGULANTS

i. Heparin like molecule

↓

Combine with Antithrombin-III (AT-III)

↓

Inactivate clot factors II, IX to XII

ii. Thrombomodulin (TM)

Thrombin (Pro-coagulant)

↓ TM

Thrombin [ant-coagulant type)

↓ ⊕

Protein-C & Protein-S

↓

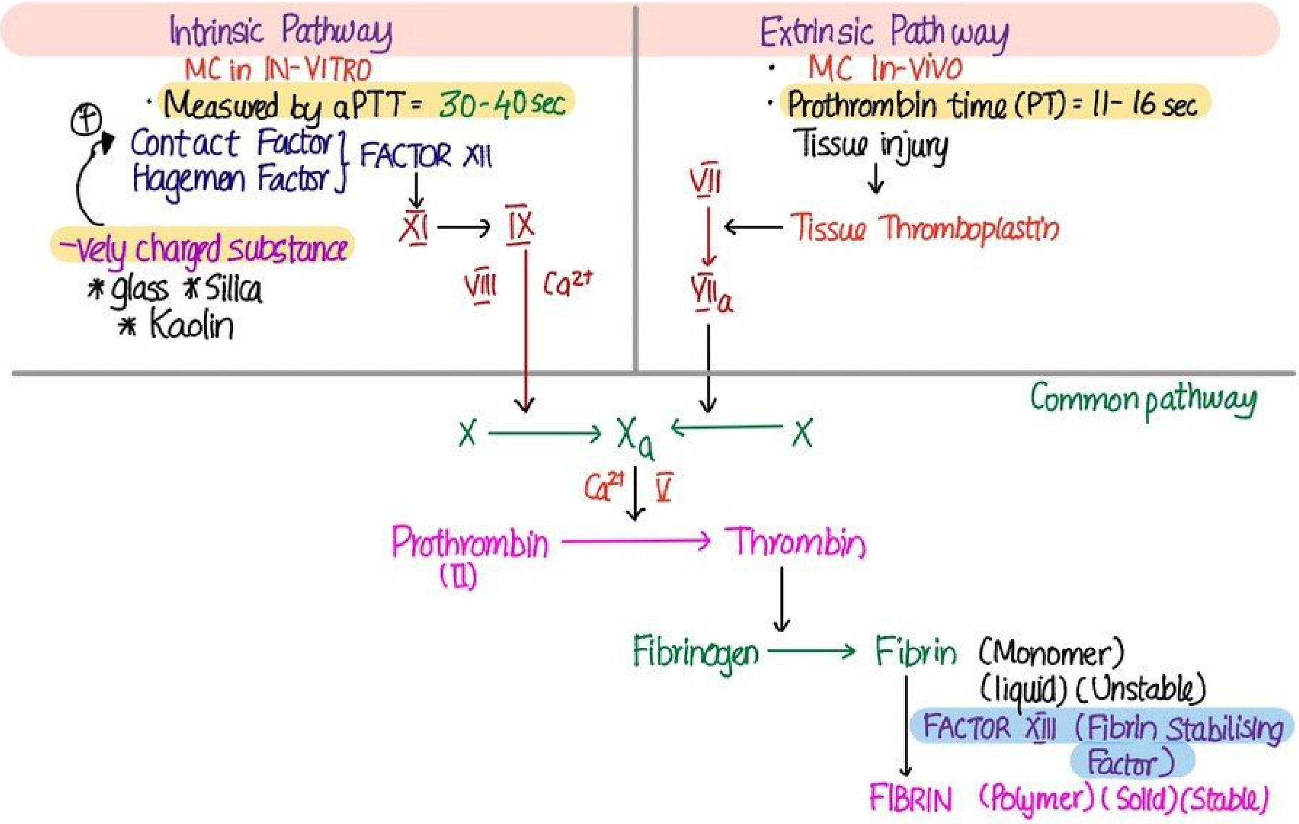
degradation of Factor V, VIII

Factor V mutation (LEIDEN-MUTATION)

↓

↑ Thrombosis in young patient in arterial & venous aka Activate Protein C Resistance Syn.

Coagulation Pathway



FIBRIN ⟶ Clots $\xrightarrow[\text{Clot Lysis}]{\text{PLASMIN}}$ FIBRIN-DEGRADATION PRODUCTS (FDP)

Routine-Protocols

i. Plastic syringes & vials should be used
ii. Sample must be processed within 2 hrs
iii. Must be kept at Room temperature (20-25°C)
EXCEPT : • Anti-Phospholipid Antibody Syndrome } Kept @ 4°C
• Factor assay
iv. Platelet poor plasma is used for coagulation studies
EXCEPT in Platelet disordes use Platelet rich plasma is used.
v. BEST Anticoagulat for Coagulation studies : 3.2% Trisodium Citrate
for ESR (i) Westergren method : 3.2% Trisodium Citrate
(ii) Wintrobe method : Oxalate (disodium/di K⁺)
for CBC : EDTA (∵ RBC morphology Presered)
for ABG : HEPARIN
↓
BEST For i. Electrolyte
ii. Osmotic Fragility Test
iii. Leukocyte defect
iv. Immunopherotyping

BLEEDING & COAGULATION DISORDER

Approach :

Minor Bleeding
- Petechiae & Purpura on Skin or mucosa
- Platelet disorders
Ⓝ Platelet count : 1.5-4.5 lacs/mm³
① Thrombocytopenia : <1.5 lacs/mm³
② Bleeding Time : Ⓝ = 2-9 min
if platelet count is normal
Then it's platelet functional disorder

Major Bleeding
- Spontaneous hematoma within muscles.
- Bleeding into joints /Hemarthrosis
- Clot factor disorders
Here go for PT & aPTT

Clot Factor Disorders

HEMOPHILIA

A : VIII deficient
- X-linked Recessive
- M>F
- MC Presentation : Hemarthrosis
- No petachiae & Purpura

B : IX deficient (↱ Christmas Factor)
- X-linked Recessive
- M>F
- MC Presentation : Hemarthrosis
- No petachiae & Purpura

C : XI deficient
- Autosomal recessive
- MC present : Asymptomatic

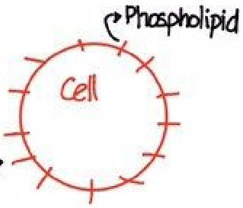
Lab Findings :
- Platelet count } Normal
- B.T } Normal
- VIII, IX, XI ↓↓ : ∴ aPTT prolonged & PT Normal
  ∴ Isolated aPTT prolongation
- INVESTIGATION OF CHOICE : FACTOR ASSAY (Quantitative analysis of clot factor)
  HERE SAMPLE KEPT @ 4°C

Acquired Factor Inhibitors

- These are autoimmune disorder
- F>M
- Pathogenesis : • Auto antibodies directed against clot factors
  ↓ MC
  VIII
- These are a/w
  - i. Autoimmune disorder Eg: SLE
  - ii. Pregnancy & post partum
  - iii. Disseminated malignancies
- Clinical Features : Hemarthrosis → Joint pain
- Investigation : MIXING TEST

Antiphospholipid Antibody Syndrome - APLA

- It's a Autoimmune disorder
- Ab formed against cell membrane
  MC protein associated with APLA Syn. = β_2-glycoprotein



- F>M
- Hyper coagulable state → Recurrent arterial & venous thrombosis.
- Clinical Features :
  - i. Brain : Seizures & stroke
  - ii. Heart : M.I
  - iii. Skin : Livedo Reticularis
  - iv. Pregnancy : Eclampsia
    Recurrent foetal losses
  - v. DIC like features
- Diagnosis :
  - i. aPTT prolongation > PT Prolongation
  - ii. Dilute Russel Viper test

CONFIRMATION:

1 Clinical criteria + 1 Lab Criteria

① Vascular events : evidence of art/venous Thrombosis
② Pregnancy Related Unexplained foetal losses
a) ≥3 in <10wks of gestational life
b) ≥1 in <10wks of gestational life
>1 premature birth before 34 wks of Gestational life

- 3 Abs : ↑↑ in more than 2 ocassions & it should be done on 12wk interval
  - i) Anti-Cardiolipin Ab
  - ii) Lupus - Anticoagulant
  - iii) Anti - β_1 Glycoprotein

aPTT ↑ : Isolated Prolongation of aPTT

Bleeding
i. Hemophilia A, B, C
ii. Acquired Factor inhibitors

Non-Bleeding deficiency
i. APLA Syndrome
(Lupus anticoagulant)

∴ BEST INVESTIGATION FOR Isolated prolongation of aPTT } MIXING TEST

Take → 1 : 1 Plasma
Patient Normal

Hemophilia
↓ add
1 : 1 Plasma
Patient Normal
↓
aPTT Normal

Acquired Factor inhibitors
↓ add
1 : 1 Plasma
Patient Normal
↓
initially : Ⓝ aPTT
later : ↑ aPTT
∵ ab start to destroy

APLA Syndrome
↓ add
1 : 1 Plasma
Patient Normal
↓
NO EFFECT
∴ Persistent Prolongation of aPTT
↓ add Phospholipid
Normalised

Disseminated Intravascular Coagulation - DIC

- also known as Consumptive Coagulopathy
  ∵ there will be destruction of both Platelet & clot fact.
- Pathogenesis : Endothelial damage / tissue damage
  ↓
  Release Tissue factor / Thromboplastin
  ↓
  Hyper activation of coagulation pathway
  +
  destruction of platelet
- Lab Finding :
  - ↑ amount of Fibrin Degradation Products
  - S. Fibrinogen decreased.
  - Both intrinsic & extrinsic pathway damage
    ↓
    ↑ aPTT & PT
  - MOST SENSITIVE TEST : ↑ FDP
  - MOST SPECIFIC TEST } D-DIMER
    BEST INVESTIGATION }
  - Platelet ↓ : BT Prolongation

MCC of DIC : OBG related > Sepsis / Trauma

Platelet Disorders

QUANTITATIVE

- Platelet count = ↓
  B.T = prolonged

Thrombocytopenia

Amegakaryocytic

* Bone-marrow is defective
  ↓
  ↓ megakaryocyte
* Peripheral Blood = ↓ plat. count

Eg: Aplastic Anemia
Myelopthisic anemia
Chemotherapy
Radiotherapy

Megakaryocytic

* BM : Normal
* P.B : ↑ platelet destruction

∴ BM Compensate
↓
↑ megakaryocyte

① Immunogenic
Ab destroy plat.
Eg: ITP (Immunogenic/Idiopathic Thrombocytopenic Purpura)
Infections : HIV
A.I dis. : SLE
Coomb's T : +ve

② Non-immunogenic
HUS (Hemolytic Uremic Syndrome)
TTP (Thrombotic Thrombocytopenic purpura)
Coomb's Test : -ve

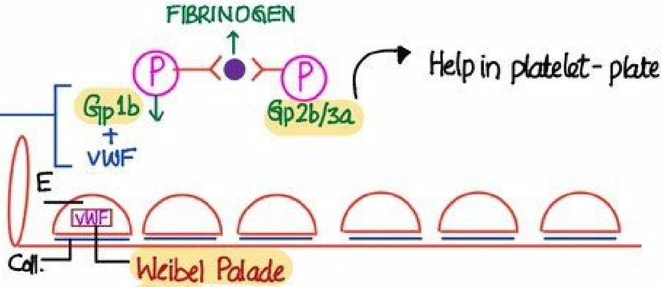
QUALITATIVE

- Platelet count is normal
- BT = ↑ (∵ of functional defect)
- aka Platelet Functional Defect Disorders

Eg: i. Bernard-Soulier Disease
ii. Glanzman's Thrombasthenia
iii. Von-Willebrand disease

Platelet Functional Disorders

Adhesion
* Platelet to vessel wall by Gp1b & vWF



Help in platelet-platelet : Aggregation

Weibel Palade Body
* Present in E
* Contain vWF: Richest source
  ↳ Synthesised by : * Endothelium
  * Megakaryocytes (Rare)

INVESTIGATIONS

① Platelet Aggregation Test
- Done by ADP, Collagen, Epinephrin
- Interpretion — Normal
  — Defective

② Ristocetin Adhesion Test (RAT)

↓

is a drug ⟶ induce Gp1b

RAT ⊕ : Normal

RAT ⊖ : Abnormal

Bernard-Soulier's Disease

- Rare AR
- Gp1b is defective : ∴ Adhesion disorder
  Gp2b/Gp3a is normal.
- Large platelets on Peripheral smear
- Clinical Features : Petachiae
  Purpura

Labfindings :
- PT } Normal
- aPTT } Normal
- RAT is abnormal i.e negative
- PAT c̄ ADP, Collagen, Epinephrin : Normal
- BT prolonged
- may have Mild plat count ↓

Von-Willebrand Disease

- MC inherited Bleeding disorder
- MC pattern of inheritance : AD
- MC subtype : Type-1
- Most severe subtype : Type-3
- Deficiency of vWF
  ↳ Help in (i) Platelet adhesion
  (ii) Stabilise Factor VIII : Most important func.
- Lab finding :
  - PT : Normal
  - aPTT : Prolonged
  - PAT : Normal
  - BT : ↑
  - RAT : -ve/abnormal

Glanzman's Thrombasthenia

↓

Platelet aggregation defect

- Rare AR
- Gp2b/3a : defect ↗
  Gp1b : Normal

* Clinical Features : Bleeding at Umblical cord stump in neonates

- Lab Finding :
  - PT } Normal
  - aPTT } Normal
  - PAT : Defective/Abnormal
  - BT : Prolonged
  - RAT : +ve : Normal

Thrombocytopenia

1. Immunogenic / Idiopathic Thrombocytopenic Purpura : ITP

- Pathology : IgG Ab destroying Platelets
  ↓
  ↑ Platelet destruction
  ↓
  BT ↑ ; Platelet ↓

ACUTE	CHRONIC
- Pediatric	- 40 yr & above
- M=F	- F>M
- d/t viral inf.	- Spleen is site of platelet destruction
- Spontaneous recovering within 6 months	

SPLEEN : Ⓝ Size — ITP, Aplastic Anemia

- Investigation of choice : Coomb's Test ⊕

TTP

* affect arterioles & cappillaries
* defect in ADAMTS-13 ↓↓
  ↓
  Ⓝ : Prevents Platelet Aggregation
* ↑ Plat. aggregation → ↑ plat. destruction
  ↓
  Thrombi
* Clinical features :

PENTARD OF TTP
- i. Thrombocytopenia
- ii. In small vessel c̄ Thrombi
  ↓
  RBC passage obstruction
  ↓
  Fragmentation of RBC
  ↓
  Microangiopathic Hemolytic Anemia (MAHA)
- iii. Thrombi in Kidney : ARF
- iv. CNS : neurological deficits
- v. Fever

HUS

* affect arterioles & cappillaries
* ADAM TS-13 Normal
* 2 Types

TYPICAL

* Pediatric (<2yrs)
* 2° to GIT inf/Lung
  ↓
  followed by diarrhea
  ∴ aka D^+ type HUS
* MC due to VEROTOXIN of E. Coli O157-H7
* can also by
  - i. Shigella
  - ii. Strep. Pneumonia
* Clinical Features

TRIAD
- i. Plat. count ↓
- ii. MAHA
- iii. ARF : More prominent

- iv. CNS Invol.
- v. Fever

} Less Prominent

ATYPICAL

* Adults
* No GIT inf/Lung inf.
* Etiology :
  - i. Complement Factor def
    MC : Factor H def
  - ii. A.I dis.
  - iii. Disseminated malignancy

No diarrhea
∴ D^- type HUS

* Clinical Features
  ↓
  Pentard of TTP
* FLOW CYTOMETRY
  ADAMTS-13
  - Ⓝ : HUS
  - ↓ : TTP

TRANSFUSION MEDICINE / BLOOD BANKING

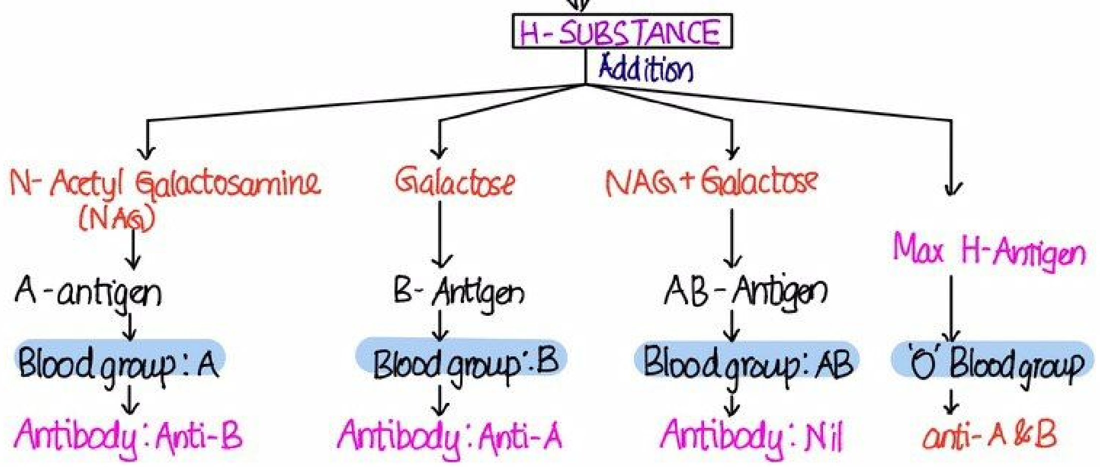
ABO BLOOD GROUP

- A,B antigen encoding gene present on Chromosome 9
- Pattern of inheritance : Co-dominant inheritance
- H Gene on Chr 19

↓ have

Fucosyl-transferase activity i.e FUCOSE

+ Glycolipid / Glycoprotein



⇓

H-SUBSTANCE

Addition

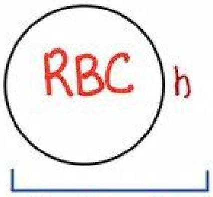
- N-Acetyl Galactosamine (NAG) → A-antigen → Blood group : A → Antibody : Anti-B
- Galactose → B-Antigen → Blood group : B → Antibody : Anti-A
- NAG + Galactose → AB-Antigen → Blood group : AB → Antibody : Nil
- Max H-Antigen → 'O' Blood group → anti-A & B

- DETECTING ANTIGEN ON SURFACE is called as FORWARD GROUPING
  DETECTING ANTIBODY IN SERUM is called as REVERSE GROUPING

⊛ A,B, H Ag ⟹ can be present on
* RBC surface
* Serum
* Body fluids ∴ ABO is called SECRETORS
  EXCEPT CSF

BOMBAY BLOOD GROUP

- a/w Chr 19
- 1952 , Bhende discovered
- AR & No H gene



Bombay Blood Group

No-H gene
↓
AR
↓
hh'

- ∴ No A,B, H Antigen
  ∴ called as NON-SECRETORS
- Serum : anti-A, anti-B, anti-H Antibody
  ∴ NEVER give O blood group to this patient
  ∴ Require transfusion from another Bombay Blood grp donor.

Blood Bank

Donor ———→ Blood Donation ⇒ Blood components seperation within 6 hrs
* completed within 8-10 min

Blood Components:

	STORAGE TEMP	SHEL-LIFE
Whole Blood	2°-6°C	42days
i) Packed RBC (PRBC)	2°-6°C	42days
ii) Platelets	20-25°C : Room temp with continous Agitations	5 days
iii) Fresh Frozen Plasma (FFP)	−18°C or lower	1yr
iv) Cryoprecipitates (Clot factor)	−18°C or lower	1yr

Preservatives

i. ACD : For 21 days
ii. CPD : For 21 days
iii CPD-A : For 35days
iv. SAGAM : For 42 days

Routine - Protocoal : Blood Transfusion

i. Whole Blood / Packed RBC :

- Blood Transfusion should start within 30min.
- Prolongation: causes bacterial contamination in room temperature
- Transfusion should be completed within 4 hrs

Needles used : 18-19 G

Filter-Size of transfusion set } 170µm

Role

i. Glucose : → Nutrition to RBC by Glycolysis

ii. Phosphate : → Buffers to maintain pH (lacticacid of Glycoly)

iii Citrate : → for chelation of Ca^{2+} i.e to prevent clotting within Blood bag

Excessive citrate : Hypocalcemia (tetany)

iv. Adenine : → Add ATP & Stabilise RBC membrane ∴ ↑ shelf life

v. Saline : → For maintaing normal isotonicity of RBC

vi. Mannitol : → Prevent Hemolysis

Indications

i. Whole Blood : HYPOVOLEMIC SHOCK due to trauma
ii. Packed RBC : For anemia correction
iii. Platelets : Platelet disorders (Dengue/malaria)
iv. FFP : They have multiple clot factors
Trauma with multiple clot factor deficiency
v. Cryoprecipitate (Powder form) : Contain Factor VIII, XIII, Fibrinogen, vWF
i. Hemophilia A
ii. Von Willebrand Disease
iii. Afibrigenemia

IMMUNOLOGY

IMMUNITY

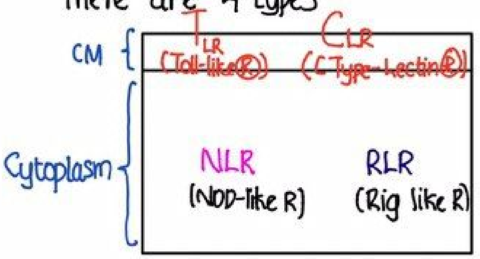
INNATE

- Since birth
- No previous exposure
- No immunological memory
- Non- Specific

Components

i. Epithelial cell
ii. Neutrophil
iii. Macrophages
iv. Dendritic cells
v. NK cells
vi. C- Reactive Proteins
v. Complements
vi Pattern Recognition Receptors (PRR)

- There are 4 types



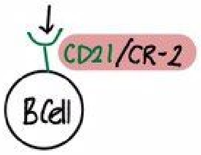
- BEST DEFINED : TLR
- CLR formed against : Fungal infection
- RLR formed against : Viral infection
- NLR formed against : i. Flagellin
  ii. ↑ metabolic byproducts (Eg: Uric acid)
  iii. Ionic disturbances (Eg: Na^+/K^+ Imbalance)

ADAPTIVE

- Acquired
- previous exposure ⊕
- Immunogical memory present
- Specific

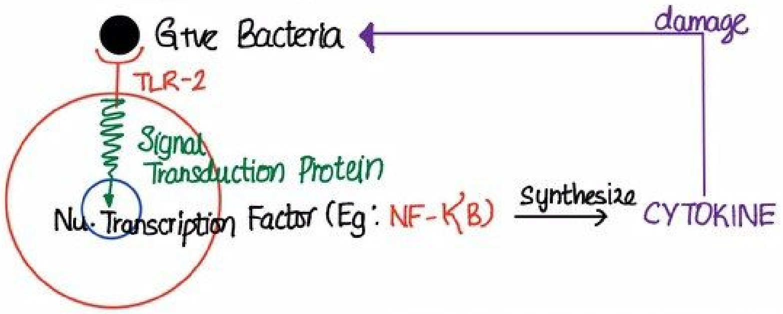
Components

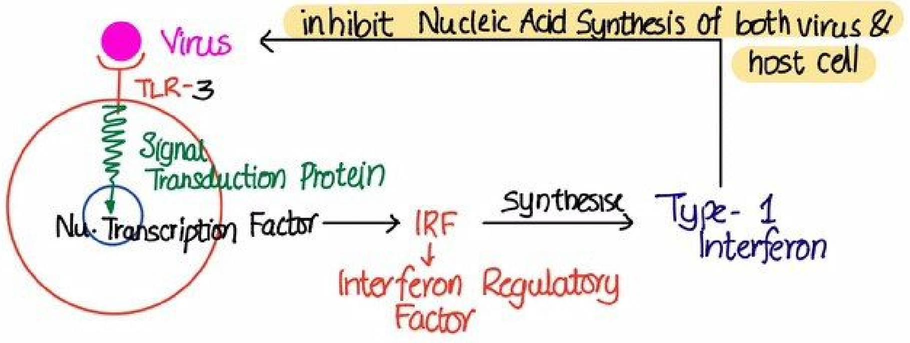
i. B-Cell (Humoral)
ii. T- Cell (Cellular)
NK/T cell is a subset of T cells
iii. MHC
iv. Complements
Eg: EBV



Toll -Like Receptor :

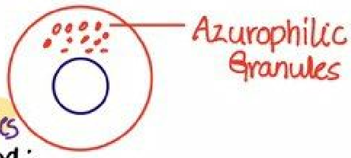
- There are 11 types of TLR
- TLR-1 /2 : Gram +ve Bacteria, Leptospira endotoxin.
  TLR- 4 : Gram -ve Endotoxin
  TLR- 3 : Viral DNA
- Mechanism of action :
  ⇒ Location : Epithelial cell, Endothelial cells, APC (Eg: Dendritic cell)




Virus
inhibit Nucleic Acid Synthesis of both virus & host cell
TLR-3
Signal Transduction Protein
Nu.
Transcription Factor
IRF
Interferon Regulatory Factor
Synthesise
Type-1 Interferon

TYPES OF IMMUNE CELLS

- Lymphocytes
  - T-Lymphocytes
    - * Peripheral Blood: Maximum (70%)
  - B-Lymphocytes
    - * Peripheral Blood: 20%
  - Innate Lymphoid Cells (ILC)
    - ↓ NK-Cell aka Large Granular Lymphocytes
    - - Peripheral Blood: 5-10%
- Antigen Presenting Cells

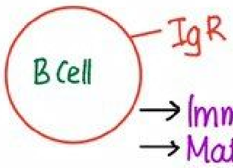


ORIGIN OF B & T CELLS

Mature cells: CD34 −

Bone-Marrow
↓
Stem cells (Immature cell: CD34+)
↓
Common Lymphoid Progenitor cells

if it express PAX-5
↓



→ Immature cell: IgM_R
→ Mature B cell: IgM/D_R (both)
→ Activated B cell: $IgM/D/A_R$ (all)

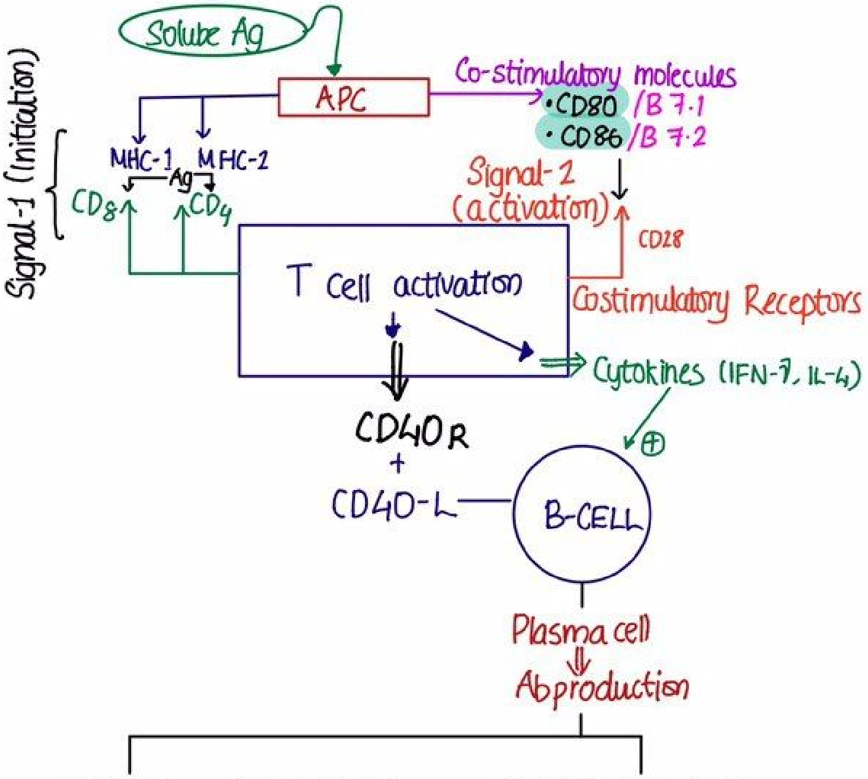
if it express NOTCH gene
↓

Immunophenotype : CD 10, 19-24
pan B cell marker : CD 19

Immunophenotype CD 1-8
CD 28
Pan T Cell marker : CD3

	T CELL	B CELL
* Site of origin :	Bone - Marrow	Bone - Marrow
* Site of maturation/ Central organ :	Thymus	Bone - marrow

Soluble Ag can't be identified by TCR



T-Cell dependent method
- MC (>90%)
- Memory ⊕
- Stronger

T-Cell independent
- <10%
- No memory
- Weak Ab

Anergy : Permenent inactivation of Both Tcell & Bcell d/t lack of co-stimulatory interaction

Eg : i. Tcell CD80/ CD86 + $CD28_R$
This interaction will not develop
ii. B cell $CD40_L$ with $CD40_R$
This interaction will not develop

* It's a mechanism to prevent auto immunity in Peripheral Blood (Periph. Tolerance)

MHC Restriction :
CD4 accept antigen only from MHC-II
CD8 accept antigen only from MHC-I

CLASSIFICATION OF T-CELL

- Helper T cell (CD_4T) ; 60%
  - Memory
  - Effector
    - T_{H1}
    - T_{H2}
    - T_{H3}
  - Regulatory / CD_4 Treg
- CYTOTOXIC T CELL / CD_8T : 30%

Regulatory T Cell (CD_4T_{Reg})

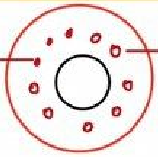
Peripheral Blood
↓
Self-Ag
↓
CD_4T_{Reg}
expression — CD25
expression — FOXP3 → Mutation leads to IPEX Syndrome

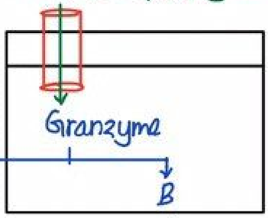
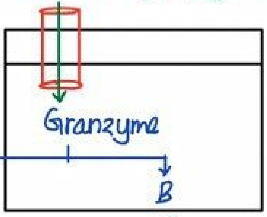
- Immunological dysreg.
- Polyendocrinopathy
- Enteropathy
- X-linked.

CD25, FOXP3 → Synthesis of anti-inflammatory Cytokines (IL-4,6,10, TGF-β)
↓ ⊖
prevent proliferation & differentiation of auto reactive cell [= Peripheral Tolerance]

CD25 mutation leads to : Multiple Sclerosis

* M.O.A :



CD8 T Cells	NK cell
Granules ↓ Rupture ↓ Perforin-Granzyme System	Granules ↓ Rupture ↓ Perforin-Granzyme System
	
Granzyme A → form Free-Radical → destruction B → Fas/Fas-L induction → Apoptosis	Granzyme A → form Free-Radical → destruction B → Fas/Fas-L induction → Apoptosis

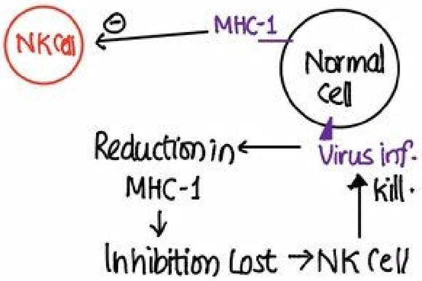
CD_8 T Cells NK Cell

functional Similarity (CD_8 >NK cell)

i. Killing of Virus infected cell
ii. Killing of Tu. Cell
iii. Killing of Graft cell

* CD16
CD56 ⇒ F_c -IgG -Cell
Ab depend. Cellular Cytotoxicity
present in * NK cells
* Eosinophil.
* neutrophil

*



EFFECTOR T-CELL

TH1
IFN-γ → ⊕ TH1
↓ secrete
IFN-γ, IL-2, 12
↓ ⊕
Macrophage
* function of TH1 cell = function Macrophage
i. Granuloma formation
ii. Intracellular killing
iii. Delayed: Type-4 HSR

TH2
IL-4 → ⊕ TH2
↓ secrete
IL-4, 5, 6, 13
↓ ↓ ↓
Mastcell E Plasma cell
* functions:
i. Type 1 HSR
ii. Parascite killing
iii. IgE Ab synthesis

TH17
* a/w Autoimmunity
IL-1
IL-6
TGF-β } ⊕ TH_{17}
↓ secrete
IL-17, 22
* functions:
i. Severe Inflammation
ii. N° & Monocyte predominant
iii. a/w Auto immune disorder
Eg: Rheumatic Arthritis
Psoriatric Arthritis.

CD_4/CD_8
↙ MCH-2 ↓ MHC-I ↘
⇒ αβ-Receptors
⇒ δγ T cell (Delta-Gamma T cell)
↓
- No association with MHC
- Combine with antigen without using MHC
- neither CD_4 nor CD_8

ANTIGEN PRESENTING/PROCESSING CELL -APC

Professional

* require MHC-II & Complements

* i. Immature Dendritic cell
ii. Mature Dendritic cell (most potent)
iii. Macrophage
iv. B Cells

# T Cells & it's precurssors can never become an APC

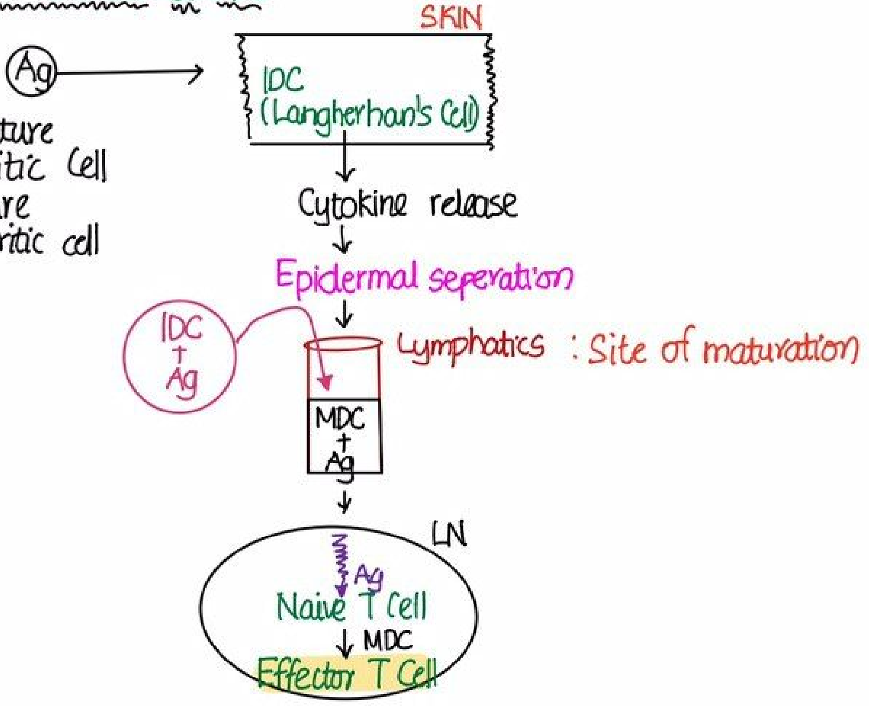
Non Professional

* already No MHC II molecule but under the influence of cytokine during inflamation
↓ Eg: IFN-γ
induce MHC-II molecule.

* i. Endothelial cells
ii. all types Glial cells (i.e astrocytes, oligodendrocytes or ependymal cells)
iii. Epithelial cells (few)
Thymic epithelial cells
Thymocytes : precurssor of T cell
↓
∴ Not an APC
M-Cells
→ • Microfold cells
• Present on Peyer's patches
iv. Fibroblast
v. Pancreatic Islet cells

SITE OF MATURATION OF APC

# IDC : Immature Dentritic Cell
MDC : Mature Dendritic cell



MAJOR HISTOCOMPACTIBILITY COMPLEX

- aka Human Leuckocyte Antigen

APC — MHC (gene I, II, III)
↓
Chromosome 6p
⇓

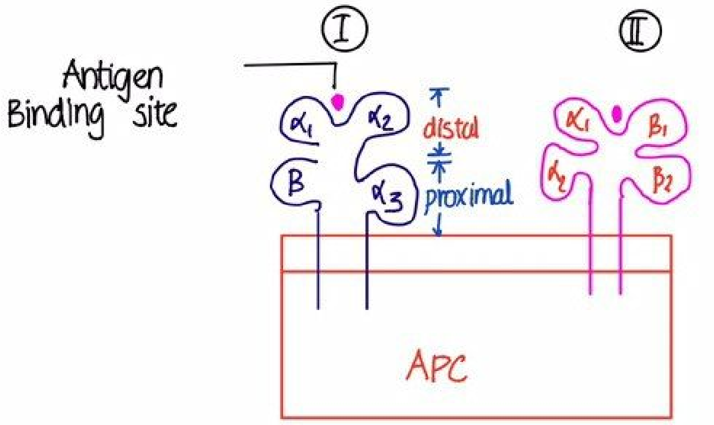
I
- * Ag
  ↓ presenting to
  CD_8 T
- * present on
  Nucleated cell,
  Platelets
- * α - Chain
  ↓ encoded by
  HLA A, B, C

III
- * a/w Auto immune disease
- * encodes
  - C_2, C_4, properdin
  - Factor-B
  - Heat-shock proteins
  - TNF-α

II
- * Ag
  ↓ presenting to
  CD_4T
- * present on B cell (Both I & II)
  Dendritic cell (Both I & II)
  Macrophage (Both I & II)
- * Detection : Mixed Lymphocyte Reaction
- * HLA-D
  - DP
  - DQ
  - DR

Before organ transplantation : HLA matching done
↓
Most important HLA in this : DR > B > A > C
↓
Best

DR is best ∵ it reduce the risk of Hyperacute Graft rejection



Antigen Binding site : $\alpha_1 - \alpha_2$ $\alpha_1 - \beta_1$

HYPER SENSITIVITY REACTION

- Excessive Responce to any antigenic stimulus
- 4 Types

TYPE-I HSR

- aka Immediate type of HSR
- Ag = Allergens

Ist exposure

Ag

↓ ⊕

CD₄ TH₂

↓

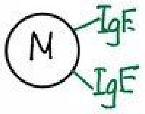
IL-4, 5, 6, 13 release

↓ ↓ ↓

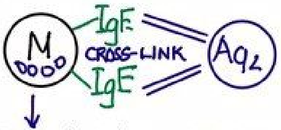
Mast cell E° Plasma cells

↓ ↓

Sensitisation Synthesize IgE Ab



2nd Exposure / Re exposure



↓

Cross linking activate Mast cell

↓

Rupture of granule : Degranulation

↓

Release inflammatory mediators

PRE-FORMED
- Histamine / Serotin
- Heparin

⇓

Immediate phase of HSR
(start within 5-30 min over by 60 min)

Clinical features:
- ↑ vasodilation
- ↑ vas. permebility
- ↑ Broncho constriction

NEWLY SYNTHE SIZED
- Cytokine (IL-4,5,6 TNFα)
- Lipid mediators (LTA₄, B₄, D₄ / PGD₂)

⇓

LATE PHASE OF HSR
(Starts from 2-24 hrs persist upto days)

Clinical features are more exaggerated

* IL-5

↓ ⊕

E° → Cytokines → Inflammation + Tissue damage

Eg: 1. Anaphylaxis

- can be due to i) Drugs : PENCILLIN
  ii) Bee-sting
  iii) Food

2. Asthma
3. Urticaria
4. Prausnitz - Kusther Reaction

TYPE-II HSR

- aka Antibody mediated HSR

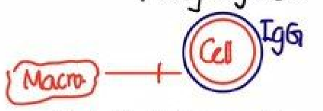
Ab IgG $\xrightarrow{\text{coating}}$

↱ Type-V HSR
(Variant of Type II HSR)

- 3 mechanism

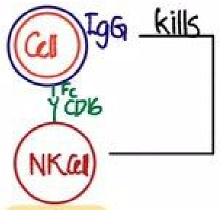
① OPSONISATION

Phagocytosis



Eg: • Autoimmune Hemolytic anemia
• Auto immune thrombo cytopenia

Killing without Phagocytosis



ADCC
Ab-dependent-Cellular Cytotoxicity

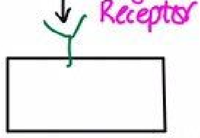
② Inflammation

IgG/IgM
↓ deposit

↓ ⊕
Complement pathway
↓
C5a
C3a } Anaphylotoxin
↓
Neutrophil Chemotaxis
↓
FR & Enzymes
↓
Inflammatory damage

Eg: i. Good Pasture Syndrome
ii. Pemphigus Vulgaris

③ Cellular Dysfunction
↓
No cell damage &
No inflammation
- IgM/IgG
↓ damage Receptor



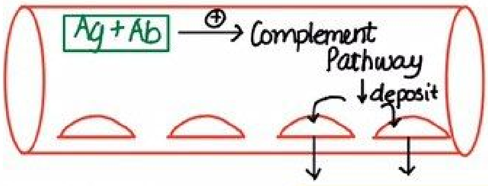
Receptor mediated damage
↓
Cellular dysfunction

Eg: i. Grave's disease
damage TSH Ⓡ
↓
↑ T_3 & T_4
ii. Myasthenia Gravis
damage ACh Receptors

TYPE-III HSR

- aka Immune complex mediated HSR

1. Vasculitis (PAN)



Immune complex mediated damage

2. Glomerulonephritis
3. Arthus reaction (localised serum sickness)

TYPE-IV HSR

- aka Cell mediated HSR

CD4 T (Helper)

TH1
Granuloma : TB
Contact dermatitis
Rheumatoid arthritis

TH2
Chronic allergic Rhinitis
Chronic allergic Asthma

TH17
Rheumatoid arthritis
Contact dermatitis with severe inflammation

CD8 T (Cytotoxic)
Graf Rejection
Graf V/S Host disease

GRAFT TYPES

1. **Autograft**
   ↓
   Graft placed on same individual & it's from one area to another part of Body
2. **Syngeneic/Isograft**
   ↓
   Graft taken from identical twins/clones
3. **Allograft**
   ↓
   Graft from Non-identical individual within same species
4. **Xenograft**
   Graft from Another Species

TYPES OF GRAFT REJECTIONS

1. Hyperacute Graft rejection
   - happens within minutes
   - d/t Preformed antibodies from
     - i. Previous Blood transfusion
     - ii. Previous grafts
     - iii. Multiparous preg. females

   ↓
   ∴ Eg: of Type II HSR
   - MC a/w RENAL TRANSPLANTATION
2. Acute Graft Rejection
   - starts from weeks to months
   - 2 possibilities

   Acute Humoral Graft Rejection
   - * Type-II HSR >> Type IV HSR
   - * Classical deposition on Blood vessels : C4d complement

   Acute Cellular Graft Rejection
   - * by CD_4 T & CD_8 T
     ∴ Type IV HSR
3. Chronic Graft Rejection
   - * CD_4 & CD_8 T cell involvement : ∴ Type IV HSR
   - * moths to years
4. Graft Versus Host Disease (GVHD)
   - In sheeps & cattles it's called as Runt's disease
   - Donor is immunocompotent
     Host is immuno deficient } → GVHD
   - MC a/w Allogenic stem cell transplantation
   - CD_4 & CD_8 T are involved
     MHC I & II are involved } Type IV HSR
   - Most commonly a/w CMV infection

GVHD

ACUTE
- * rejection <100 days
- * Liver
  S.I
  Skin (MC effected) : Erythematous → S/C Fibrosis + Calcification (like SCLERODERMA)
  Lungs (Rarely effected)

CHRONIC
- * rejection >100days

Adverse Reactions / Transfusion Reaction

- Most common transfution Reaction : Febrile Non-hemolytic Tran. Reaction
  - ∴ No Hemoglobinuria / No Hemosiderenuria
  - → is ∵ of LEUKOCYTES by releasing Cytokines (IL-1,6)
- Infections : • Hepatitis B ≫ Hepatitis C
  - → MC transfusion transmitted Hepatitis
  - • HIV infection • CMV infection
  - • Malaria • EBV with infectious mononucleosis (Rare)
  - → Transmitted through all Blood components ∵ of Malarial Trophozoites. it can withstand extremes of temperature
- Most common cause of Death in Blood Transfusion : TRALI (Transfusion Related Acute Lung Injury)

Criteria for TRALI : Should start within 6 hours.

CROSS-MATCHING is not required for : Platelets & Cryoprecipitates

ABO matching is required for : FFP

Massive Blood Transfusion

- Definition : >1 Blood volume of transfusion within 24 hours
  - ↓ i.e >5 Liters or >10 Blood Bag
- Complication :
  - i. Citrate will cause : Chelation of Calcium ↓ HYPOCALCEMIA
  - ii. ↑ citrate $\xrightarrow[\text{Metabolism}]{\text{Liver}}$ ↑ HCO_3^- : METABOLIC ALKALOSIS
  - iii. Metabolic Alkalosis → HYPOKALEMIA
  - iv. HYPERKALEMIA < HYPOKALEMIA
  - v. HYPOTHERMIA
  - vi. Dilutional thrombocytopenia (↓ Platelet d/t ↓ life span)
  - vii. MCC of death : Dilutional Coagulopathy
    - ↓ can precipitate
  - viii. DIC

In massive Blood transfusion follow : Fixed Blood Component

first give RBC → PLASMA → PLATELET

1 : 1 : 1

MECHANISM OF AUTOIMMUNITY

- Autoimmunity : Loss of immunological tolerance (IT)

↳ Non responsivness to self antigen

↓ CENTRAL TOLERANCE ↓ PERIPHERAL TOLERANCE

CENTRAL TOLERANCE

a) Central Deletion / Negative Selection

* Auto reactive cell in B.M / Thymus
↓
Killed by Apoptosis

* Negative selection : Negatives will be selected & killed

⊛ In Thymus

AIRE (Autoimmune Regulator Gene)
↓ induce
Self antigen
↓
to identify auto reactive T-Cell
↓
Killed by apoptosis.

Mutation in AIRE : Autoimmune Poly endocrinopathy

b) Central Editing / Receptor editing

In B.M

BCell — R Responsive + Self antigen
↓
Receptor editing $\xrightarrow{\text{if fails}}$ Apoptosis
↓ to
R Non-responsive

PERIPHERAL TOLERANCE

a) Anergy
b) Regulatory T-Cell (= CD_4 Treg)
c) Induction of apoptosis
d) Antigen sequestration
↓

⊛ discrete mass of antigen not exposed to Blood/Lymph
Such organs are called as Immune previleged organs

↳ # Brain
# Eye → Traumatic uveitis
# Testis (Seminiferous tubules)
↳ Traumatic orchitis

ETIOPATHOGENESIS OF AUTOIMMUNE DISORDER

- Multifactorial

1. GENETICS

MHC Gene

- * HLA-B-27 : Ankylosing Spondylitis
- * HLA-DR-4 : Most strongly a/w Rheumatoid Arthritis
- * HLA-CW_6 : Psoriasis

Non-MHC Gene

- * Most Common Gene : PTPN-22 gene polymorphism
  Eg: RA, Psoriasis, DM Multiple sclerosis
- * CD25/IL-2 R polymorphism : Multiple Sclerosis
- * NOD-2 gene
  Crohn's disease

2. ENVIORNMENTAL

a) Radiation

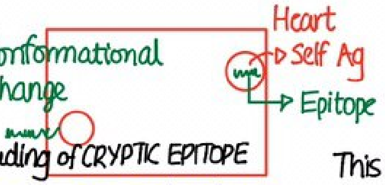
UV light on cell
↓
Cell damage
↓
Nu. antigen exposure
↓
Anti nuclear Ab formed

b) Infections

- * DM d/t Coxsackie ds
- * Rheumatic Heart disease d/t streptococcal infection
- * Molecular mimicry / Cross-reactivity is the mechanism behind these disorders

Molecular mimicry in Rheumatic Heart Disease

Streptococal Antigen
↓
Toxin :→ Conformational Change



Spreading of CRYPTIC EPITOPE

Epitope : protein part of Ag which will combine with Ab
This is called Cryptic Epitope as it's hidden

Mol. structure of Str. Ag & cryptic epitope are similar
↓
CROSS-REACTION / MOLECULAR Mimicry

Autoimmune disorders (AI) : Female > Male } MC
: 20-40 yrs } MC

SYSTEMIC LUPUS ERYTHEMATOSUS

- Pathogenesis : Multifactorial

GENETICS	IMMUNOLOGICAL FACTORS	ENVIORNMENTAL
↓ i) TREX-1 ii) HLA DQ (MHC-II) ⇓ Synthesis of autobandies like Smith Ab/dsDNA Ab iii) Early complement deficiency	* Inappropriate B cell activation (d/t Nu. Ag)	* Radiations like UV Rays * EBV infection

- Clinical Features :

M - Malar Rash
D - Discoid Rash
S - Serositis
  - a) Lung : Pleuritis (MC)
  - b) Heart : Pericarditis (MC)
    Most charachteristic : Libman-Sac Endocarditis
O - Oral ulcers
A - Arthritis (Non-erosive)
P - Photosensitivity

B - Blood : MC Autoimmune Hemolytic Anemia
R - Renal involvement
A - Anti-nuclear Ab
I - Immunological : Smith Ab, dsDNA Ab
N - Neurological : Eg: Psychosis

i. Photosensitivity : SSA Ab/ Ro Ab ↑
ii. Pericarditis : SSA Ab/ Ro Ab ↑
iii. Shrinking Lung Syndrome : SSA Ab/ Ro Ab ↑
iv. Neonatal lupus with Congenital Heart Block : SSA Ab ≫ SSB Ab
↓Ro ≫ ↓LA

Reynaud's Phenomenon : Exposure to colder area
↓
a/w anti-U_1 RNP
(Ribo nucleo protein)

↓
P - Pallor
C - Cyanosis
R - Reddness

Psychosis corresponds to : anti-Ribosomal P-Ab

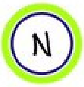
- Diagnosis : Auto antibodies

1. Serology
   - Most sensitive : ANA
   - Most specific : Smith Ab

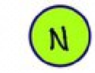
	Smith	ds DNA
Sensitivity:	30%	70%
Specificity:	>95%	90%

   - Best for Prognosis corelation & diagnosis } ds DNA

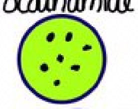
2. Indirect immunofluorescence
5 patterns
i) Rim/ Peripheral Pattern
MC a/w dsDNA



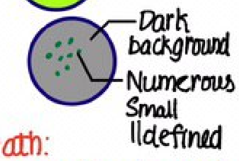
ii) Diffuse / Homogenous Pattern
MC a/w anti-Histone Ab
↓
a/w DSLE : Hydrolazine
Procainamide
CNS/Renal involΘ ← DSLE



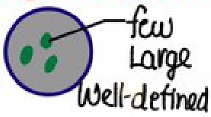
iii) Speckled Pattern :
MC a/w Smith Ab



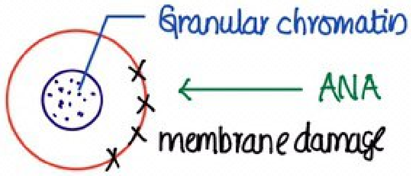
iv) Centromeric pattern :
anti centromere Ab
(Scleroderma) → MCC of death: Pulmonary involvement



v) Nucleolar pattern :
Scleroderma, Sjorgen syn.
(MC)



Peripheral Smear :

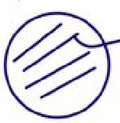


↓

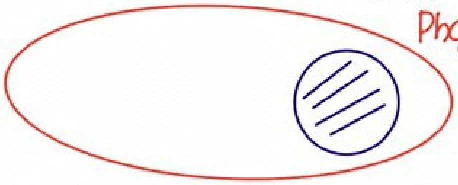
Exposure of Nucleus

Seen in :
- Peripheral Blood
- Bone marrow

LE-Bodies / Hematoxylin Bodies



⇓ taken up by



LE - Cell : LE Bodies + Phagocyte

Cause of death : Most common cause

- Within 10yrs of onset → Renal Failure
- Overall → Cardiac Failure (Inflammatory cell → damage endothelium → Atherosclerosis)

SCLERODERMA

- aka Systemic Sclerosis
  ↳ ↑ collagen deposition on dermis
- F>M, 20-40yrs
- Pathogenesis : Microvascular injury
  ⇓
  inflammatory cell
  ↓
  Endothelial damage
  ↓
  Platelet activation
  ↓
  Fibrogenic cytokine TGF-β release
  ↓
  Subcutaneous fibrosis + calcification

- Clinical Presentation :

A. Diffuse

- Cutaneous : Early
  Widespread
- Visceral : Early
  Widespread

* Anti-DNA Topoisoisomerase Ab (Scl-70)

* RNA polymerase-III Ab
↓
a/w
- Acute renal crisis
- RCC

* Fibrillarin seen
Anti-U_3 RNP Ab

* Most sensitive Ab :
Anti nuclear Ab

* Most specific Ab
Topo Isomerase Ab

b. Localised

} LIMITED

* CREST Synd.
Calcinosis
Raynaud's pheno : Earliest finding
Eosophagel dysmotility : Most sever
Sclerodactyly
Telangiectasia

* Anti- centromere Ab is seen

- Biopsy finding : i. Subcutaneous fibrosis
  ii. Calcification
  MCC of death : Pulmonary involvement

SJOGREN SYNDROME

- F > M : 40-60 yrs
- Immune mediated lacrimal & salivary glands
- 2 types :

1° Sjogren Syndrome

Ab damage

Glandular invol.
i) Lacrimal gland
↓
Dry eyes
(Keratoconjuctivitis sicca)
ii) Salivary gland
(MC: Minor salivary glands of lips)
Dry mouth
(Xerostomia)

Extraglandular invol.
i) Nonspecific Hepatitis
ii) Arthris/Arthralgia : MC Extraglandular manifestation
iii) Marginal zone B cell Lymphoma

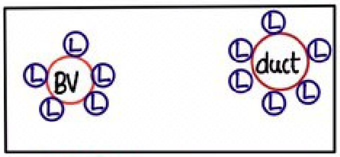
2° Sjogren Syndrome

- a/w A.I Disorder
  MC a/w Rheumatoid arthritis
  >70% of patients have Rheumatoid Factors
  ↓
  IgM ab directed against Fc IgG
- a/w SLE
- a/w Chronic active hepatitis
  older name of A.I Hepatitis

- Diagnosis :

A. Biopsy finding

Best site : Minor salivary gland



Earliest finding: Perivascular & Periductal Lymphocytic infiltarate

B Serology finding

* Anti-nuclear Ab seen

i. SS-A (Ro)
Most sensitivity
Corelate to a. Early onset
b. Longer duration
c. Extraglandular involvement.

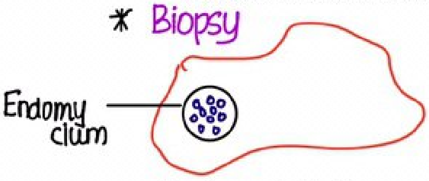
ii. SS-B (LA)
Most Specific

INFLAMMATORY MYOPATHY / MYOSITIS

- immunologically mediated inflammatory disorders of muscles
- It consists

A. Poly myositis

* C/f:
Proximal mu. weakness
* Biopsy



Endomycial inflammation
+
No vasculitis

B. Dermatomyositis

* MC type
* MC type a/w paraneoplastic syndrome
* C/f:

i. Proximal mu. weakness
+
Cutaneous involvement

① ii. Heliotropic rash :
Purple/red periorbital rash with edema

iii. Gottron's papules:
scaly erythematous lesions on Knuckles & elbow joint

⇒ Anti-Mi-2 Ab present

② i. Interstitial Lung disease/ Arthritis
(Mechanic's Hand)
Roughneing & cracking on hand giving rise to irregular dirty lines

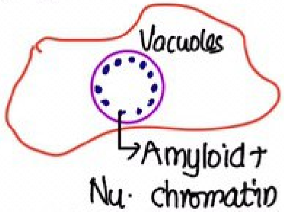
⇒ Anti-JO-1 ab aka Anti-Histidyl t-RNA Synthase Ab

③ Juvenile DM/Paraneoplastic type of DM

⇒ anti P_{155}/P_{140} Ab

C. Inclusion Body myositis

* MC type beyond 50yrs age.
* involve
distal muscle weakness
* Biopsy



Basophilic-rimmed vacuoles

∴ +ve for Congo-red positive

- Biopsy of Dermatomyositis : i. Perifascicular Lymphocytic Infiltarate → causing atrophy
  ii. Vasculitis

RHEUMATOID ARTHRITIS

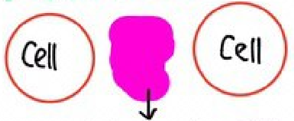
- Chronic inflammatory disorder. Autoimmune origin
- F > M, 40-60 yrs

# a/w HLA DR4 : Most strongly associated
PTPN-22 polymorphism

- Clinical Features : * B/L symmetrical involvement of smaller joints (usually spare distal IP joints)
  - * 1. Swan-neck deformity
    - distal I.P with flexion
    - proximal I.P with hyper extension
  - 2. Boutnniere deformity
    - distal I.P with hyperextension
    - proximal I.P with hyperflexion
  - 3. X-Ray Report
    - Radial deviation of wrist
    - Fingers showing ulnar
- Diagnosis
  - A. Biopsy
    - i. Pannus : Swollen, edematous Synovium
      Rich in inflammatory cells
      Fibroblast
      Granulation tissue
      ↓
      Causing destruction of articular cartilage
    - ii. Rheumatoid S.C Nodules
      - central area with Fibrinoid necrosis
      - surrounded by palisaded macrophage
  - B. Serology
    - i. Rhematoid Factor
    - ii. Most specific : Anti cyclic citrullinated peptide (CCP) (95%)

AMYLOIDOSIS

- Amyloid : insoluble fibrillary glycoproteins
  ↳ Morphology :



pink, eosinophilic, acellular
Extracellular material } AMYLOID

↑ amyloid → Pressure atrophy

- Properties of amyloid :

A. Physical Properties

* ↕ ↕ ↕
  - Length : Indefinite
  - Non branching fibril
  - diameter - 7.5 to 10nm

↓ Seen on Electron microscopy

* By X-Ray difraction method/ Infrared spectroscopy

↓

β-Pleated sheet (3° conformation)

↓

∴ Congo red positive confirmed

- Under Ordinary light (LM)
  - Red/ Pink
  - ↓ Nondiagnostic as it can be
    - i) Collagen
    - ii) Fibrin
    - iii) Hyaline
    - iv) Amyloid
- Polarised light/ Polarised micro.
  - Apple green birefringence
  - ↓ Confirm Amyloid

B. Chemical Properties

* Consists of
  - i) Fibril (95%)
  - ii) P-component & other glycoprotein

↓ Stabilise Amyloid

↓ in extracellular matrix

* Stains :
  - a) Congo red positive
  - b) Methyl violet
  - c) Crystal violet
  - d) Thioflavin T
  - e) Toluidine Blue → Mast cell in BM

Silver methanamine never used for Amyloid

bcoz, silver will form black precipitate & hide amyloid

Pathogenesis :

- Amyloidosis is a/w Chromosome 21
- d/t Misfolding of protein
  - ① Excessive protein production → Misfolding → Amyloid production
  - ② Mutant protein in normal quantity but prone to misfolding
    Eg: Trans thyretin

Classification of Amyloidosis :

- SYSTEMIC
  - Primary Amyloidosis
  - Secondary Amyloidosis
  - Hemo dialysis a/w
  - Heredo familial Amyloidosis
- LOCALISED

PRIMARY AMYLOIDOSIS

- MC Type of amyloidosis
- AL Type accumulation [L= ↗ Light chain of immunoglobulin]

- Usually a/w Plasma cell disorders (Eg: Multiple Myeloma)
  Gingival amyloidosis seen in Multiple myeloma

SECONDARY AMYLOIDOSIS

- 2° to chronic inflammation
  ↓
  IL-1, 6, TNFα
  ↓
  ↑ serum amyloid associated protein
  ↓
  AA type

- MC a/w Rheumatoid arthritis
- also a/w TB, Osteomyelitis, Bronchiectasis

* Paraneoplastic Syndrome a/w : AA Type
seen in : i. RCC
ii. Hodgkin's Lymphoma

HEMODIALYSIS A/W

- a/w $A\beta_2$ micro globulin in Joints, Synovium, Tendon
  ↓ pressure atrophy of median nerve
  Carpel Tunnel Syn.

HEREDOFAMILIAL AMYLOIDOSIS

a. Familial Meditaranean fever
  - Pyrin protein effected
  - AA type

b. Familial Amyloidotic Polyneuropathy
  - mutant transthyrectin deposition

c. Senile cardia Amyloidosis
  - wild type /non mutant transthyre

LOCALISED AMYLOIDOSIS

- deposition on

① Brain
  a) Alzheimer's disease : $A\beta$ amyloid
  b) Prion disease : $APrP^{sc}$ amyloid

② Endocrine
  a) ACal : Familial medullary carcinoma of thyroid
     Calcitonin
  b) AIAPP : Type-2 DM
     Islet associated Poly Peptide

ORGANS :

- MC / M·seriously a/w organ : Kidney
  - → MC presentation: Massive proteinuria > HTN
  - → Earliest site : Mesangial matrix > Capi·Mem.
- Spleen

A. Diffuse	B. Localised
• Red-Pulp affected • aka Lardaceous spleen	• follicle affected • Sago spleen

- Liver : Usually LFT normal till the end. Earliest site of deposition : Space of disse

DIAGNOSIS :

A. Biopsy	B. Stain
* MC site / Best site : Abd fat pad aspirate ≫ Rectal Biopsy Abd fat pad aspirate ↓ Sensitivity : 80% Comfortable Rectal Biopsy ↓ 60% uncomfortable	* Congo-red on Polarised Microscope

Patient with massive proteinuria. All other system normal. In this ideal site for biopsy : Kidney / Renal biopsy as it's case of Isolated Organ Amyloidosis.

MCC of death in : a) Primary Amyloidosis : Cardiac Failure
b) Secondary Amyloidosis : Renal Failure
OVERALL : Cardiac Failure

IMMUNODEFICIENCY DISORDERS

- PRIMARY
  - • Hereditary
  - • 6 months to 2 yrs
  - Innate immunity
    - ① Complement def. (C_2, C_4)
    - ② Macrophage Chronic granum·dis·
    - ③ LAD I/II/III
  - Adaptive immunity
    - i) B cell def.
    - ii) T cell def.
    - iii) B & T cell def
- SECONDARY
  - • 2° to infection, immuno suppression, cancers
  - • Any age

B-CELL DEFECT :

1. Bruton's Agammaglobinemia
   - X-linked Re. (M>F)
   - Bruton's Tyrosine Kinase mutation

     ↓ ⊖

     Pre & Pro B cell → Mature B cell ↓

     ↓

     ↓ Plasma cell → Ab ↓
   - C/f : i) Recurrent infe. by capsulated organism
     ii) ↑ risk for Auto immune disease
     iii) T cell count will normal
2. Selective IgA deficiency disorder
   - MC 1° Immuno def. disorder
   - Naive B Cell —✕→ IgA producing B Cell

     ↓

     ↓ IgA production

     ↓ IgG_2 & IgG_4
   - C/f : i) ↓ mucosal immunity
     ii) Severe & fatal anaphylatic Reaction to Blood transfusion
     Bcoz IgA from donor behave as foreign body
     iii) ↑ risk of A.I disorder
3. Common Variable Immuno. def. disorder
   - IgG, M↓, A↓
   - Mature B cell —(diff)→ B cell

     ↓

     Affected
   - C/f : i) Recurrent infection of Giardiasis (diarrhoea)
     ii) ↑ Risk for : a) A.I disorders
     b) NHL
     c) Gastric carcinoma

T-CELL DEFECT :

1. Di George Syndrome
   - MC microdeletion syndrome

     → Chromosome 22q

     → i) TBX-1 gene : devp. of Heart & Blood Vessals
     ii) development of 3rd & 4th pharyngeal arches (Thymus & para thyroid)
   - C/f : i) Cardiac malformation (tetrology of fallot)
     ii) Thymus hypoplasia : Tcell deficiency
     iii) Hypocalcemia
     iv) Dysmorphic face.

2. Job Syndrome / Hyper IgE Syndrome
   - ↓ development of TH_{17} cell
   - ↓ IFN-γ reduced ; ↑↑ IgE
   - C/f : i) Cold abscess
     ii) Mucocutaneous candidiasis

B & T-CELL DEFECT :

1. Severe combined Immuno. def disorder
   - X linked disorder (MC),

     ↓

     defect in cytokine Ⓡ signalling

     ↓

     IL-7 Ⓡ → Lymphocyte Proliferation/diff.

     IL-15 Ⓡ → for NK cell develop

   AR

   ↓

   Defect in Adenosine Deaminase Enzyme (ADA)

   ↓

   Toxic metabolites
   i) deoxy adenosine
   ii) deoxy ATP

   ↓

   damage Lymphocyte

   - C/f : Diaper rash
     Oral candidiasis
     Failure to thrive
     } TRIAD in infants

2. Wiskott-Aldrich Syndrome
   - X-linked Recessive disorder
   - Mutation in gene encoding WASP-Protein

     ↓

     Control cytoskeleton dependentant responses i.e
     i) Cell migration
     ii) Signal transduction
   - C/f : i) Thrombocytopenia → Small platelet size
     ii) Eczema
     iii) Recurrent infections
     } TRIAD

3. Ataxia Telengiectasia Synd.
   - AR
   - Mutation of ATM gene
   - Pathology : Cell Stress

     ↓ ⊕

     ATM gene (these are stress sensors)

     ↓ signal to

     p53 $\xrightarrow{\oplus}$ Cell-cycle Checkpoint
   - C/f : i) Ataxic movement
     ii) Telengectasia : Tortous dialated Superficial Vein on face.
     iii) Recurrent infection

HUMAN IMMUNODEFICIENCY VIRUS : Secondary immunodeficiency disorder

- MCC of 2° immunodeficiency disorder
- These are Lenti virus (= Slowly replicating) Retro virus
- Chronic phase

$$\Downarrow$$

$$HIV \xrightarrow{7\text{-}10\ yrs} AIDS$$

- Mode of spread :
  - MC Sexual (M to F)
  - In pediatric Vertical transmission (Mother to child)
  - Needle stick injury (0.3% Risk)
- Epidemiology :

HIV 1	&	HIV-2
• MC HIV • Group M Subtype C in India : MC • Routine screening done in Blood Bank		• Routine screening done in Blood Bank

- Morphology : Spherical (d = 100 nm)

  3 layers
  i) Outer - Envelope :
     - consist of glycoprotein
     - derived from host cell membrane
     - inner gp-41
     - outer gp-120

  ii) Matrix : p17

  iii) Capsid : p24 Consist of 2 HIV RNA + Enzymes
  ↓
  i) Reverse transcriptase (R)
  ii) Integrase (I)
  iii) Protease (P)

- Pathogenesis : HIV - infect ⇒ Macrophage
  Dendritic Cell
  T Cell (CD_4T_H) : MC & M. Severely affected
  ↳ # never affect Naive T-Cell
  Only Memory T Cells affected

HIV ⟶ Host cell

↓ CD_4R

↓ Co-Receptor

These are chemokine Receptor
i) CCR-5 present on : Macrophage & T cell only initial time
ii) CXCR-4 : on T-cell (Severe)

Some africans are resistant to HIV d/t Chemokine Ⓡ mutation

∴ CD_4R & Co-receptor are important for infection.

NEOPLASIA

Defined as Abnormal masses of tissue growing spontaneously even after stoppage of the stimuli

Characteristic of any tumor

Tumor

Tumor Parenchyma
- consist of collagen
- ↑ collagen synthesis of tu parenchymal cell within tumor mass

↓

DESMOPLASIA

Seen in : Pancreatic adenocarcinoma
Cholangio carcinoma

Stroma
- Blood vessels + Connective tissue

1. Rate of growth will be high for tumor

Nomenclature of tumor

"oma" : suffix Eg : Seminoma
Adenoma
Carcinoma

exceptions : These are non-neoplastic
i) Hematoma
ii) Choristoma

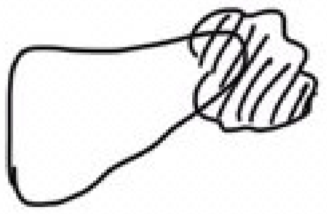
HAMARTOMA
- Considered as benign tumor
- Chromosomal abberation

↓

Monoclonality
∴ a tumor

MONOCLONALITY	POLYCLONALITY
* s/o Tumor	* s/o inflammation/infection
* All cells will be having isoenzyme	* Cells will be having different isoenzyme

CHORISTOMA	HAMARTOMA
* Tissue is normal at abnormal anatomical site	* Tissue is abnormal at normal anatomical site
* ectopic rests of normal tissue	

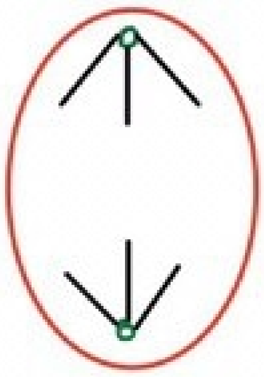


2. Mitotic figures increased
- ↑ mitotic figures can be seen in normal tissue also

Eg : Proliferating endometrium. Intestinal villi, BM cells

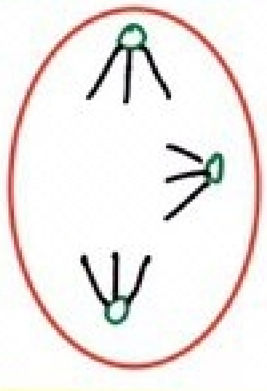
MITOTIC FIGURES

TYPICAL



Bipolar mitotic Figure
- Tumor cells
- Normal tissue

ATYPICAL



>2 poles present
Atypical M·F

Atypical M·F always sign of Neoplasia

3. Metastases : Spread of tumor to the site which are physically discontinous with primary tumor
: Sure sign of malignancy
Exceptions : i) Basal cell carcinoma of skin
Lymphatic spread is very rare
ii) Glioma
Malignant with rare/no metastases

Routes of spread :

Direct Spread
Mucinous tumor of appendix
↓
Rupture of mucin
↓
Peritoneum spread
↓
Pseudomyxoma peritonei

Lymphatic
* MC route of spread
* commonly seen in epi. cancers i.e carcinomas
Exception :
i) RCC
ii) Hepato cellular Carcinoma
} Hematogenous spread

Hematogenous
* seen in Sarcomas
Eg: Osteosarcoma
Rhabdomyo sarco.
1. Embryona RMs
2. Pleomorphic RMS
3. Alveolar RMS
↓
follow Lymphatic Spread
also by Syno vial Sarcoma

4. Loss of differentiation

- Normal tissue $\xrightarrow{\text{muta.}}$ Metaplasia $\xrightarrow{\text{muta}}$ Dysplasia $\xrightarrow{\text{muta}}$ Anaplasia $\xrightarrow{\text{mut.}}$ Tumor
- Normal tissue
↓
2 types of mutation

1. Passenger mutation
↓
giving rise to nomal phenotype cells

2. Driver mutations
↓
giving rise to malignant phenotype cells

↱ Hallmark of malignancy

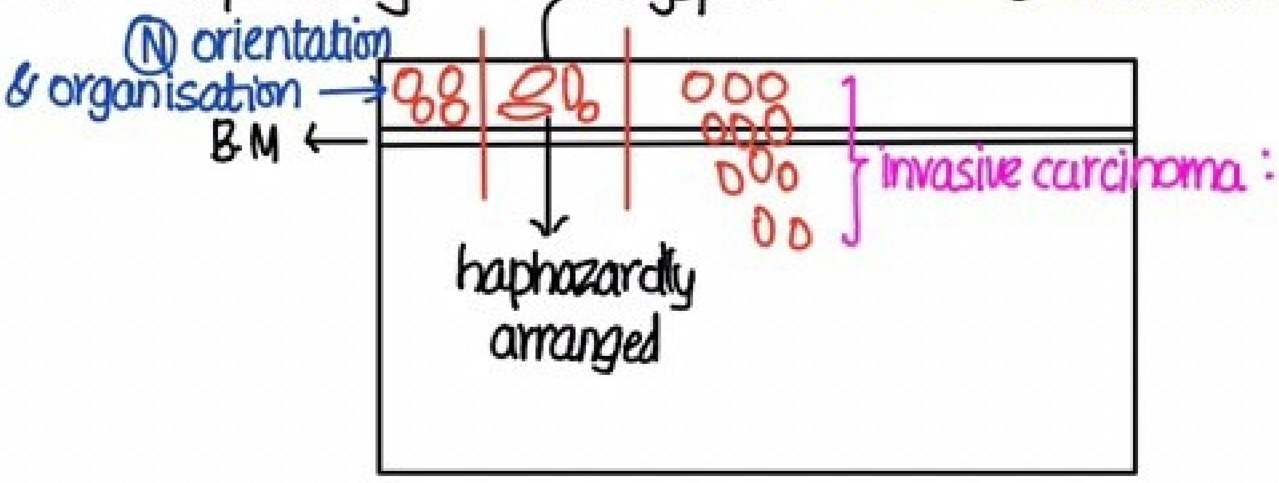
• Metaplasia ⟶	Dysplasia ⟶	Anaplasia : Complete loss of differentiation
# completely reversible	# Partially reversible	# irreversible change
# N/C = Normal	# N/C = Ratio	# N/C = Normal 1:4 ; Anaplasia 1:1
# cell polarity Normal	# altered Cell polarity	# allfered cel polarity # atypical M.F # Pleomorphisms variable shapes & size of cells or nucleus

#Cell polarity :

Dysplasia involving entire thickness of epi. & BM : Normal

↓

Called as Carcinoma Insitu



Invasive carcinoma : B.M is ruptured.

CLASSIFICATION

	BENIGN	MALIGNANT
i. Rate of growth	Normal / Limited	Very high
ii. Capsule	Well defined capsule	Ruptured / Non Encapsulated
iii. invasion	Non-Invasive No metastases	Invasive Metastatic
iv. differentiation	Well differentiated	Well differentiated to Undifferentiated
v. N/C Ratio	Intact	1:1
vi. Cell polarity	Intact	Lost
vii. Cells	uniform shape & size	Pleomorphism

CELLULAR & MOLECULAR HALLMARKS

Ⓝ : Proto oncogenes $\xrightarrow{mutation}$ Oncogenes
for cell proliferation & differentiations

1. Self-sufficiency
2. Resistant to growth inhibitory signals

↓

Tumor Suppressor Gene

3. Evasion from Apoptosis
(by increasing mechanism of anti-apoptosis

Eg : ↑ BCL-2
⊖ mitochondrial permeability

4. Limitless replicative potential

↑ Telomerase expression
- → RNA dependentant DNA Polymerase or Reverse Transcriptase
- → causes ↑ Telomere lengththening
- → Site : Germ cells, Stem cells (Abundant)

ABSENT IN Ⓝ SOMATIC CELL

if telomerase activation in somatic cell :→ Tumor cells

5. Angiogenesis

Limit of growth without blood supply : 1-2 cms

beyond 1-2cm : angiogenesis required

└ most important factor : HYPOXIA

↓

HIF - 1α gene ⊕

↓

ⓘ VEGF

ⓘⓘ bFGF

⇓

Angiogenesis

6. Metastases :

Gene
- Metastatic Signature Gene
  ↓
  promote metastases
  Eg : EZRIN (RMS & osteosarcoma)
  mir-10b
  SNAIL } BREAST CANCER
  TWIST }
- Metastatic suppressor gene
  ↓
  prevent metastases
  Eg : i) mir - 226
  ii) mir - 335
  iii) NM-23
  iv) KAI-1 (Prostate cancer)
  v) KISS (Malignanant Melanoma

Mechanism of metastases

- EMT : Epithelial Mesenchymal Transition

↓

i.e down regulation of epithelial & upregulation of mesenchymal gene

↓

Metastases

- Steps : 1. Detachement of tumor cells

Downregulation of E-cadherin

↓

Detachment

2. ECM degradation

by
- MMP -9 > 2
- Cathepsin D
- Urokinase Plasminogen activator

} ECM degradation

3. ECM - Attachment

(T) = Integrin ⇈
+
⇈ ECM Proteins : Collagen
Laminin
Vitronectin
Fibronectin

4. Vascular Dissemination & Homing of Tumor cells

Tumor cel degrades the BM & enter into Blood vessal
↓
Tumor cell form Tumor emboli
most commonly with Platelet

* moving towards organ is called homing

CCR-7 = (Tu) = CD44
CCR-7 ↓ Breast cancer
CD44 + HEV of LN

# Metastasis
i) present → Malignant
ii) absent → Benign
} Eg : Pheochromocytoma
Follicular Ca of Thyroid

7. Tumor - Metabolism
- Usually by Aerobic Glycolysis : WARBURG EFFECT
d/t AKT gene

8. Evasion from immune System

(Ca. Cells) - Ag

ANTI-TUMOR CELLS
CD8 T > Macrophage > NK cells
(Most effective)

↓

1. Antigen negative Tumor cells

2. Antigen got hidden by Glycocalyx coating

3. Cancer cells synthesize : antinflammatory cytokine (IL-10 / TGF-β)
↓
⊖ proliferation & differentiation of autoreactive cells

4. (Ca) - Ag - MHC-I ⟶ (CD8T)
⇓
Reduced MHC-I expression

5. Cancer cells induce Fas & Fas-L on antitumor cells
↓
Apoptosis.

GENES & CANCERS

micro RNA

- Tumor suppressor type microRNA
  - mir 15
  - mir16
  - ↓ mutations
  - CLL
- Oncogenic type of micro RNA
  - mir-155
  - ↓ mutation
  - B cell Lymphoma
  - mir-200
  - ↓
  - help in metastasis by EMT
- DICER
  - ↓ ⊕
  - Endonuclease
  - ↓
  - microRNA processing
  - # germline mutation in DICER
  - ↓
  - Testicular & ovarian tumor

Chromothrypsis : * Chromosomal Catastrophy

or

Chromosomal shattering

* sudden damage of large amount of chromosome

↓

Haphazard repair of chromosome

↓

i) activate oncogene

ii) inactivate tumor suppressor gene

↓

Carcinogenesis

Eg: Brain tumor like Glioma

Bone tumor like osteosarcoma

Gene-repair Defect syndrome : * aka Chromosomal instability syndrome

* AR {

Big – Bloom syndrome }

F – Fanconi's Anemia } Homologous DNA Repair defect disorder ⊕

A – Ataxia telengectasia }

X – Xeroderma pigmentosa :

AD { Lynch Syndrome

HNPCC : Hereditary Non polyposis Colorectal Ca

Xeroderma pigmentasa : Nucleotide excision repair gene Is defectective

UV light → Skin → Pyrimidine dimer

↓

Skin cancer

Nucleotide excision Repair gene ↗ remove

Lynch syndrome : Mismatch Repair gene defect

↓ Hallmark

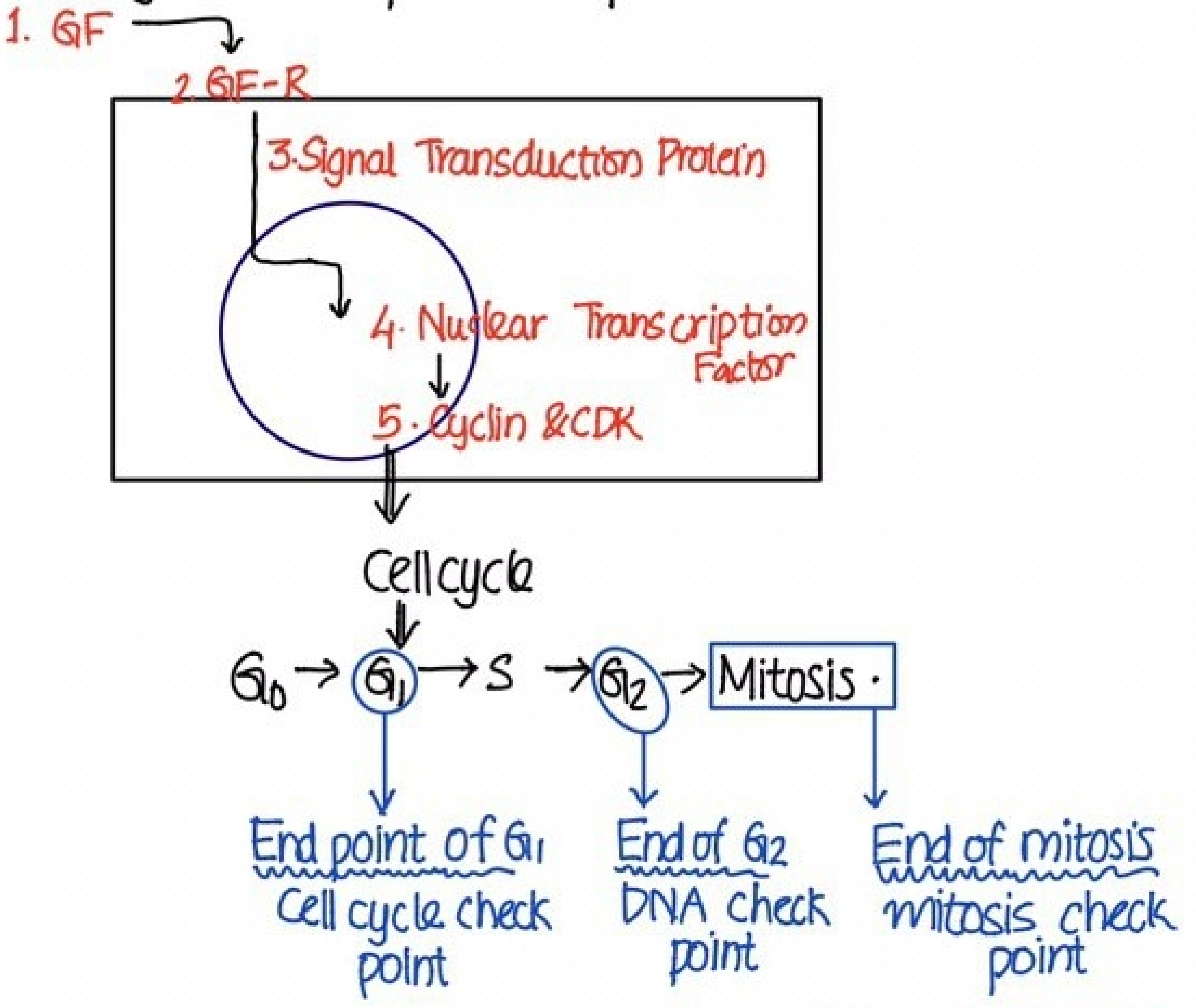
Microsatelite instability

Ⓝindvidual : Human genome Back to Back arrangement in the range of 2-6 BP
⇓
∴ constant length

Mutations in microsatellite : Microsatellite Instability
↓
a/w Colorectal cancer
Stomach cancer
Breast cancer

PROTO- ONCOGENES

- These are normal genes : help in Cell proliferation & differentiation



1 GF Protooncogenes

a) PDGF-β $\xrightarrow{\text{mutation}}$ Astrocytoma
b) TGF-α $\xrightarrow{\text{mutation}}$ Astrocytoma
c) HGF $\xrightarrow{\text{mutation}}$ HCC

2. GF-R Family

a) ERBB-1 $\xrightarrow{\text{mutation}}$ Adenocarcinoma of Lung
b) ERBB-2 $\xrightarrow{\text{mutation}}$ Breast Carcinoma
(=Her2/neu)
c) RET $\xrightarrow{\text{mutation}}$ Medullary Ca Thyroid
d) CKIT (Steel Factor) : # GIST
Seminoma
# melanoma
# myeloid cancers
↓
CD marker : CD117

3. Signal Transduction Protein

a) RAS : MC oncogene mutation in Human cancers
↓
a/w Pancreatic cancers ?
(MC mutation K-RAS > p16)

b) ABL oncogene
a/w $\frac{\text{CML}}{\text{Good}}$, $\frac{\text{AML}}{\text{Bad}}$

c) BRAF :
- >60% of melanoma case
- also a/w i) Hairy cell Leukemia (>90%)
  ii) Langerhans cell histiocytosis

4. Nuclear Transcription Factor (NTF)

MC NTF a/w Tumor: MYC

a) FOS } Leukemia / Lymphoma
b) JUN }
c) L-myc : Lung Ca
d) N-myc amplification
→ Neuroblastoma
Medulloblastoma
↓
Bad Prognosis
e) c-myc : a/w
Burkitt's Lymphoma
t(8:14)

5. Cyclin & CDK

Cyclin → Synthesised during Cell cycle movement
CDK → Already present within cells

* Cyclin D → E → A → B
$+$ $+$ $+$ $+$
Kinase 4/6 2 2 1

* Cyclin D
→ Cyclin D1/BCL-1 → Mantle cell Lymphoma
→ Cyclin D2/BCL-2 → Follicular cell Lymphoma

* CDK-4 : Glioblastoma
Melanoma

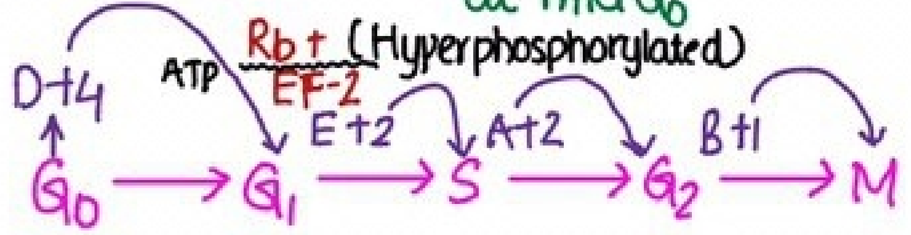
# N Cell (Inactive)

Rb + EF-2
(active)
(hypophosphorylated)

Elongation Factor-2 (EF-2)
↓
Cyclin synthesis / protein
↓
causes cell cycle movement

# Cell proliferation ⊕

Cyclin D synthesis at mid G_0 →⊕ CDK-4 → Oxidative phosphorylation
↓
Production of ATP
↓
Cell active


D+4
ATP
Rb + EF-2 (Hyperphosphorylated)
E+2
A+2
B+1
G_0 → G_1 → S → G_2 → M

[Rb] $-PO_4^{2-}$, $-PO_4^{2-}$ EF-2 is free ⟹ Cell cycle ⊕
(Inactive hyperphosphorylated)

# G_1-S transition controlled by
Hyperphosphorylated Retinoblastoma
↓
aka Molecular on-off switch
aka Governor of cell

# In cell cycle 2 checkpoint
a) G_1S checkpoint : Error before DNA replication
b) G_2M checkpoint : Error after DNA replication

Cell Cycle inhibitors :

1. Cip-Kip family
* non-specific inhibitor
i) p 21 ←⊕— p53
ii) p 27
iii) p 57
p21 →⊖ $G_1/S \gg G_2M$

2. p16-INK-4a
* specific inhibitor
Block CDK 4/6 + Cyclin D
i) p^{15}
ii) p^{16}
iii) p^{18}
iv) p^{19}

p16 INK-4a can undergo 2 mutation

- **Germline** ↓ Malignant Melanoma
- **Somatic** ↓ Cancer of
  - Breast
  - Esophagus
  - Pancreas

TUMOR SUPPRESSOR GENES

I. Mitotic Signalling inhibitors

a) APC Gene :
- aka Gatekeeper of colonic neoplasia
- mutation of APC

↓

Colon cancer

b) NF - 1 :
- Chromose 17
- Neurofibromatosis type-1
  Juvenile Myeloid Leukemia

c) NF-2 :
- Chromosome 22
- Protein : MERLIN/Schwannomin
- a/w Schwannoma
  Neurofibromatosis-2
  Meningioma

d) PTEN
- a/w Endometrial adenocarcinoma
  Cowden syndrome

II Angiogenesis inhibitors

a) VHL gene (Von hippel Lindau)

↓ mutation

Clear cell type of RCC
Cerebellar Hemangioblastoma

b) Succinate dehydrogenase (SDHB/D)

↓ mutation

Pheochromocytoma
(Paraganglioma)

III Metastic Inhibitor

CDH-1 gene (encodes E-cadherin)

↓ Mutation

Familial gastric Adenocarcinoma
Lobular Breast cancers

IV Cell Cycle inhibitors

a) CDKN2A gene

↓

encodes P16INK4a protein

↓ mutation

Melanoma
Pancreas } cancer
Eosophagus
Breast

b) Retinoblastoma (Rb Gene)
- First tumor-suppressor gene discovered
- Control G_1-S transition with inactive hyperphosphorylated RB
- Mutation : Retinoblastoma
  Osteosarcoma

V DNA Repair Gene

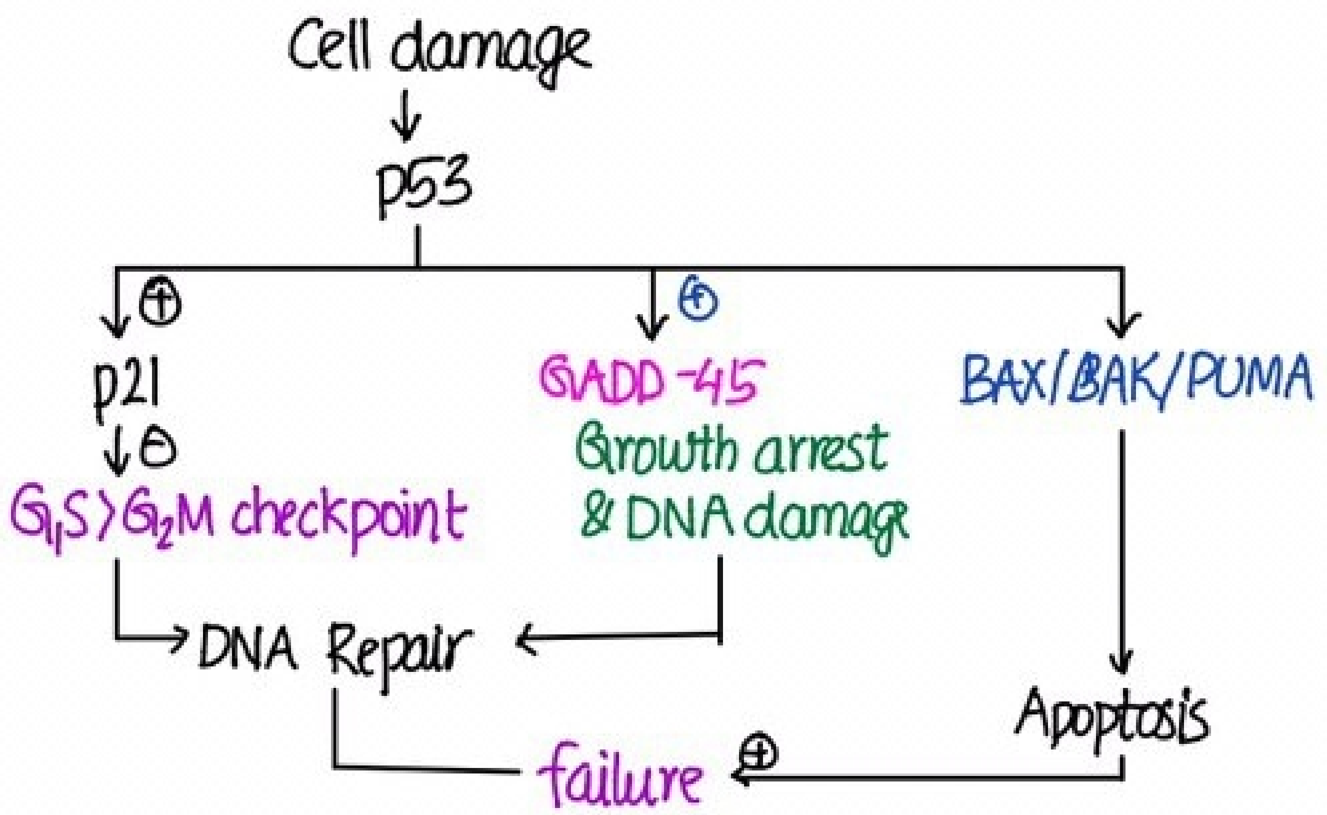
a) MSH-2,6 } mismatch repairgenes
MLH -1
↓ mutation
HNPCC

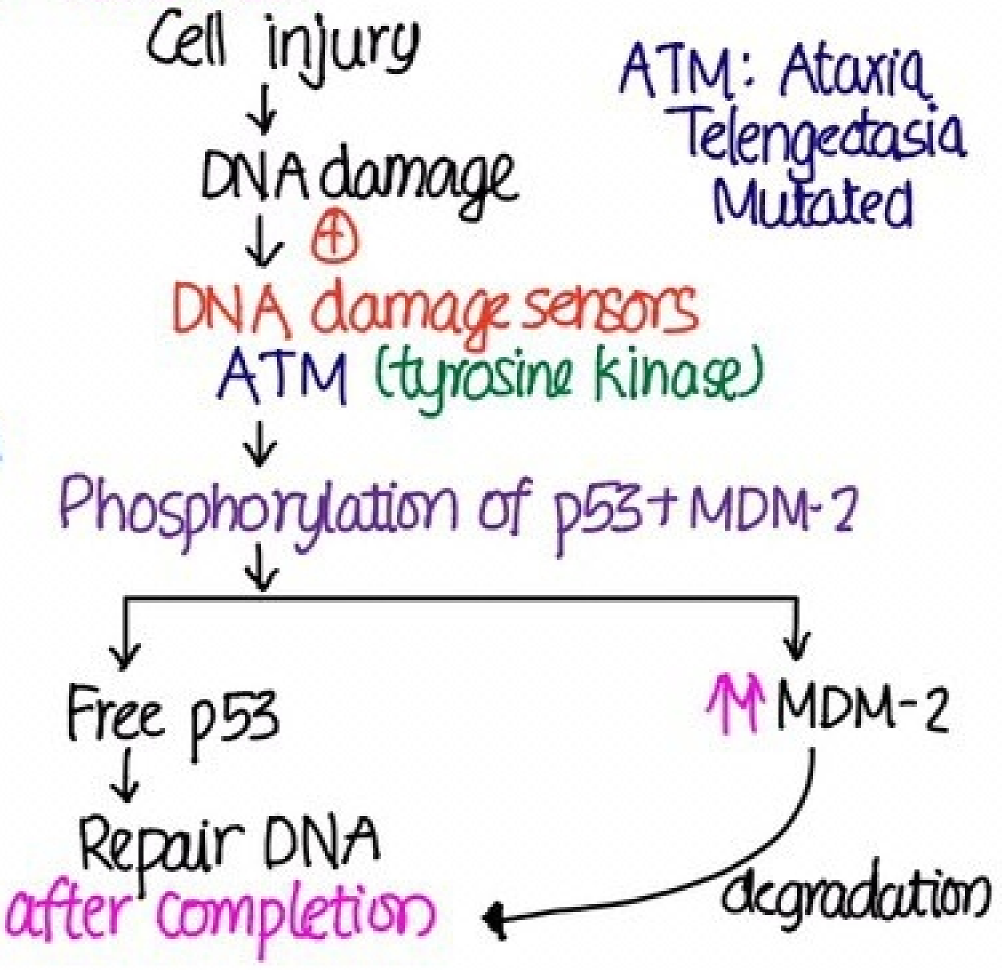
b) BRCA-1
↓
Chr 17q
• a/w
MC a/w Hereditary Breast cancers of females
Ovarian cancer

c) BRCA-2
↓
Chr 13q
MCa/w
Male breast cancer
Prostate Cancer
Pancreatic cancer

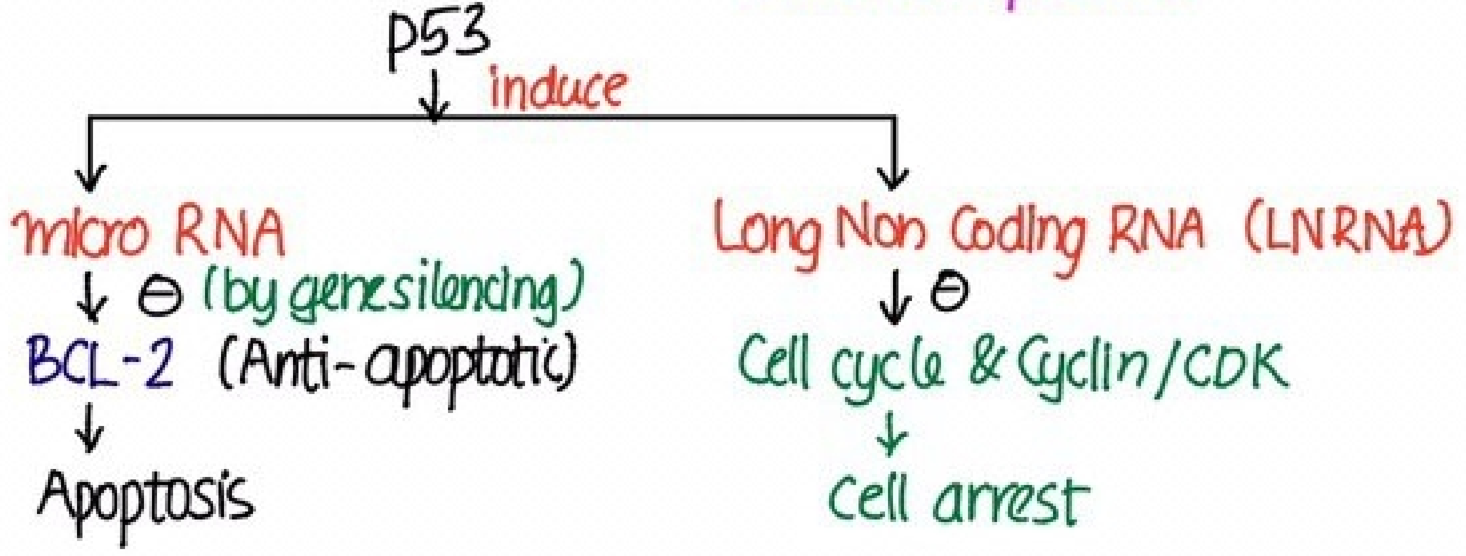
VI Genome Stabiliser ; p53

- Chromosome 17p ; MW : 53kDa
- MC gene mutation in humor cancers : >53%
- a/w Multiple Hereditary Cancer Syndrome
  ↓
  Li-fraumeni syndrome
- aka Guardian of Genome (or) Molecular Policeman

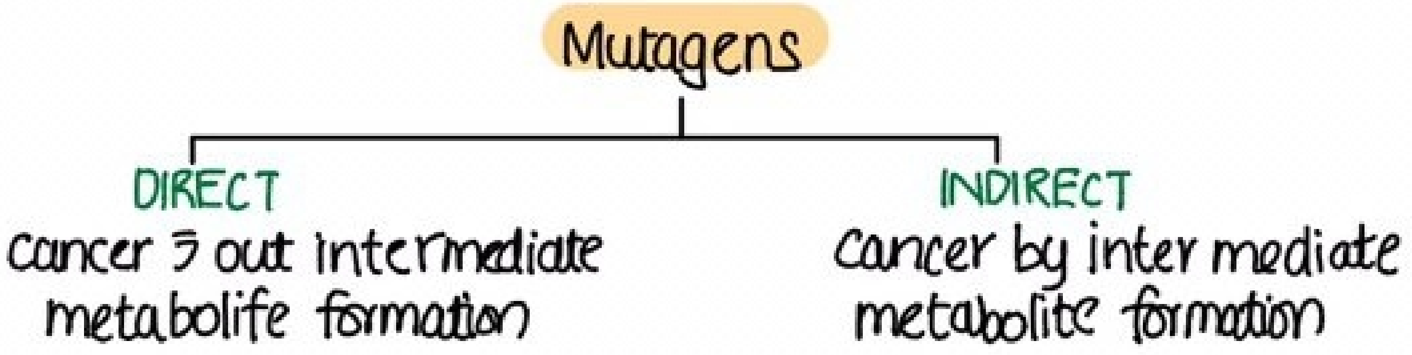




ATM: Ataxia Telengectasia Mutated



CARCINOGENESIS - CHEMICAL


Mutagens
DIRECT
cancer without intermediate metabolite formation
INDIRECT
cancer by intermediate metabolite formation

DIRECT
Eg: Chemotherapy
Alkylating agents

INDIRECT
Eg: Tobacco smoking (Benzopyrene)
↓
form epoxide
↓
Cancer

- Mutagenicity detected by AMES Test
(Salmonella typhimurium is used
Histidine ⊖

Salmonella typhimurium + Target chemical
incubated

Histidine ⊕
↓
caused mutation
∴ Mutagenic

Histidine ⊖
↓
No mutation
∴ Non mutagenic

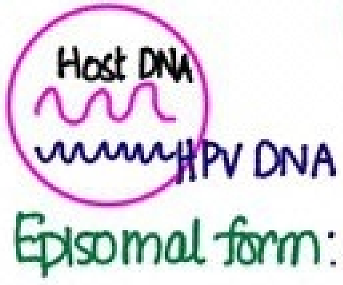
RADIATION CARCINOGENESIS

IONISING
Eg: X-Rays, α; β; γ rays
↓
d/t DNA mutation
MC cancer:
Blood Cancer > Non-hematopoeitic
↓ Blood Cancer: MC AML, CML, ALL
↓ Non-hematopoeitic: MC Papillary Ca Thyroid
Not a/w CLL

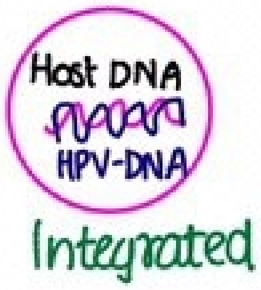
NON-IONISING
Eg: UV-light
↓
d/t Pyrimidine dimers
- MC cancer: Basal cell Ca of skin > Squamous Cell Carcinoma
- intermittent intense sun exposure (Eg: Sunbathing)
⇓
↑ risk for MC Melanoma

MICROBIAL CARCINOGENESIS

- First organism established as human carcinogen: H. pylori
  - CAG-A gene → Gastric Adeno carcinoma (MC)
  - Chronic Inflammation → NHL → DLBL > Maltoma
- Human papilloma Virus (HPV)
  Pathogenesis: 2 forms
  HOST CELL

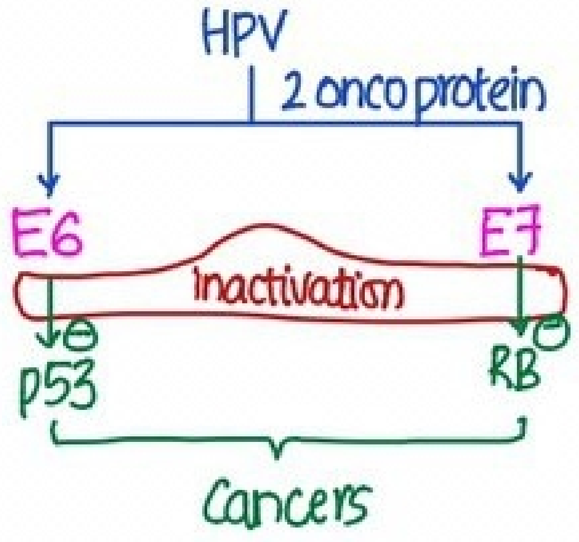


Episomal form: a/w
- Precancerous
- Papilloma

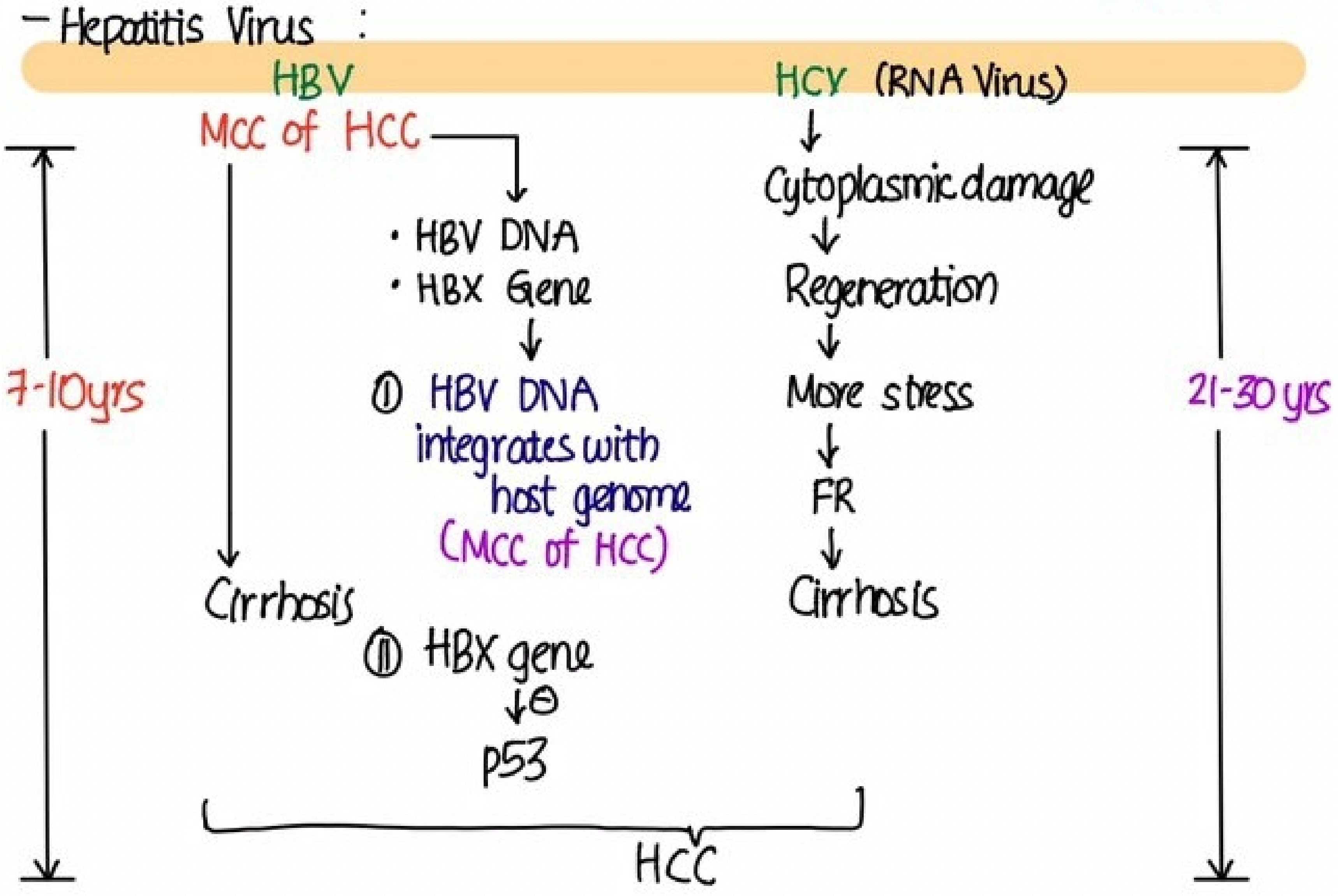


Integrated form: a/w Cancer

Episomal form : HPV 6 & 11 Integrated form : HPV 16 (MC) , 18



- Hepatitis Virus :



HBV can cause HCC without undergoing Cirrhosis also

- EBV Virus → CD21 - B Cell ⇒ a/w i) Hodgkin's Lymphoma
  - ii) NHL (Burkit's Lymphoma
  - iii) Nasopharyngeal carcinoma MC a/w EBV
  - iv) EBV m/c a/w Gastric Adenocarcinoma

- HHV-8 : a/w i) Kaposi sarcoma
  - ii) NHL (1° Effusion Lymphoma)
  - iii) Castleman disease

- HTLV-1 : a/w Adult TCell Leukemia

CLINICAL ASPECTS OF CANCER

1. Cancer Cachexia

- Loss of fats + muscle

d/t release of TNF-α

↓ ⊕

Ubiquitin Proteosome degradation pathway

↓

loss of fat + muscles

2. Paraneoplastic Syndrome (PNS)

- Symptom complexes not related to the spread of Tumor (or) hormone released from them.

(a) Endocrinopathies

i) Hypercalcemia :
- MC paraneoplastic syndrome
- d/t PTH & PTHrp (related protein)
- MC a/w Breast Ca > Lung Ca

↓

Squamous Cell Ca ≫ Small Cell Ca · of Lung

ii) Cushing syndrome :
- d/t Ectopic ACTH secretion
- MCC is Carcinoid > Small cell ca. of Lung

iii) SIADH :
- inappropriate ADH secretion
- a/w Small cell ca of Lung

⇓

MC a/w SIADH ≫ Cushing's Syndrome

(b) Hematologic

(i) Polycythemia :
- a/w Renal Cell Carcinoma
  Hepato cellular carcinoma

(ii) Trousseau's Synd. :
- Migratory superficial Thrombophlebitis
- a/w MUCIN Secreting Tumor
  - Pancreatic Adenocarcinoma
  - Prostate carcinoma
  - Lung carcinoma

(iii) Non Bacterial Thrombotic endocarditis (NBTE) :
- aka Marantic Endocarditis
- a/w Procoagulant / ↑ Estrogen release
  ⇒ Promyelocytic Leukemia

(c) Dermatologic

(i) Dermatomyositis & Polymyositis :
- a/w Gastric Ca
  Lung Ca

(ii) Acanthosis Nigricans :
- Hyper pigmented macules in axillary
- a/w Gastric adenocarcinoma
  Lung Carcinoma

(iii) Lesser Trelat sign :
- sudden seborrheic keratitis (multiple)
- a/w Glucagonoma
  (Pancreatic Cell carcinoma)

(d) Neuromuscular

(i) Myasthenia gravis :
- Ab damaging ACh receptors
- a/w
  - Thymoma
  - Lung Ca (Small cell type)

(ii) Lambert Eaton Myasthenia :
- Ab against Voltage gated Ca^{2+} channels (P/Q Type)
- a/w
  - Small cell cancer of Lungs

(iii) Opsoclonus Myoclonus synd. :
- aka Dancing Eye Dancing feet syndrome
- ab against RNA binding protein NOVA-1
- a/w NEUROBLASTOMA

(iv) Paraneoplastic Cerebellar degeneration : • Ab against Hu, Yo, Tr Antigen (Purkinje cells)
• a/w • Hodgkin's Lymphoma
  • Lung cancer

APPROACH TOWARDS TUMOR PATIENT

- Lab diagnosis

1. Look for Tumor markers
   - These are biochemical substances in human body which are increased in blood, urine, fluid or tissue
   - Source of Tumor markers : by both Tumors & Non tumor cells
   - Tumor marker shouldnot be used for confirmation of diagnosis
   - Uses : i) Screening of tumor
     ii) Assesment of prognosis
     iii) Responce to treatment
     iv) Corelate to tumor burden (size of Tu)

(a) Hormone
   (i) Calcitonin : Medullary car. of Thyroid
   (ii) 5-HIAA (5-hydroxy Indole acetic acid) : Carcinoid
   (iii) VMA Vanillyl Mandelic Acid : Paraganglioma (Pheochromocytoma)
   (iv) β-HCG ↑ Source: Syncitiotrophoblastic : • Choriocarcinoma
   Seminoma

(b) Oncofetal antigen
   (i) CEA : Colon & Pancreatic Cancers
   Breast cancer
   (ii) AFP α Feto protein : Hepatoblastoma (>90%) ≫ HCC (~70%)
   Nonseminomatous testicular malignancy

(c) Enzymes
   (i) LDH : Seminoma
   (ii) α_1-anti trypsin : Yolksac tumor of testis

(d) Tumor a/w Glycoproteins
   (i) CA 15.3 : Breast cancer
   (ii) CA 19.9 : Colon ; pancreas ca
   (iii) CA 125 : Ovarian Tumor

(e) Miscellaneous
   (i) CD 30 : Embryonal Ca of Testis
   (ii) CD 99 (MIC) : Ewing's Sarcoma
   Granulosa cell tumor of ovary
   (iii) Melanoma : Most sensitive : S100
   Most specific : HMB 45
   Mitf-1 (Microphthalmia Trascription Factor-1)
   Vimentin

(iv) Oncotype DX : Ca-Breast
(v) PAX-8 : Ovarian tumor
Thyroid tumor
(vi) Thyroid Transcription Factor-1 (TTF-1) : Thyroid cancers
Lung adenocarcinoma

2. FNAC : Fine needle aspiration Cytology

- Size of needle : 22-27 G
- Slide we see only morphology of cell only
  can't establish tumor cell relation to surrounding tissue, blood vessel, Lymphatics
- Non-diagnostic for : Follicular Ca of thyroid
  ↓
  IOC : Tissue Biopsy
  Criteria : Capsular & Vascular invasion
- C/I : i) Bleeding disorders
  ii) h/o Anaphylaxis
    → Drugs Eg: Pencillin
    → Liver Hydatid disease
  iii) Testicular malignancy
    → Indication of Testicular FNAC : Azoospermia

3. Tissue Biopsy - Histopathology

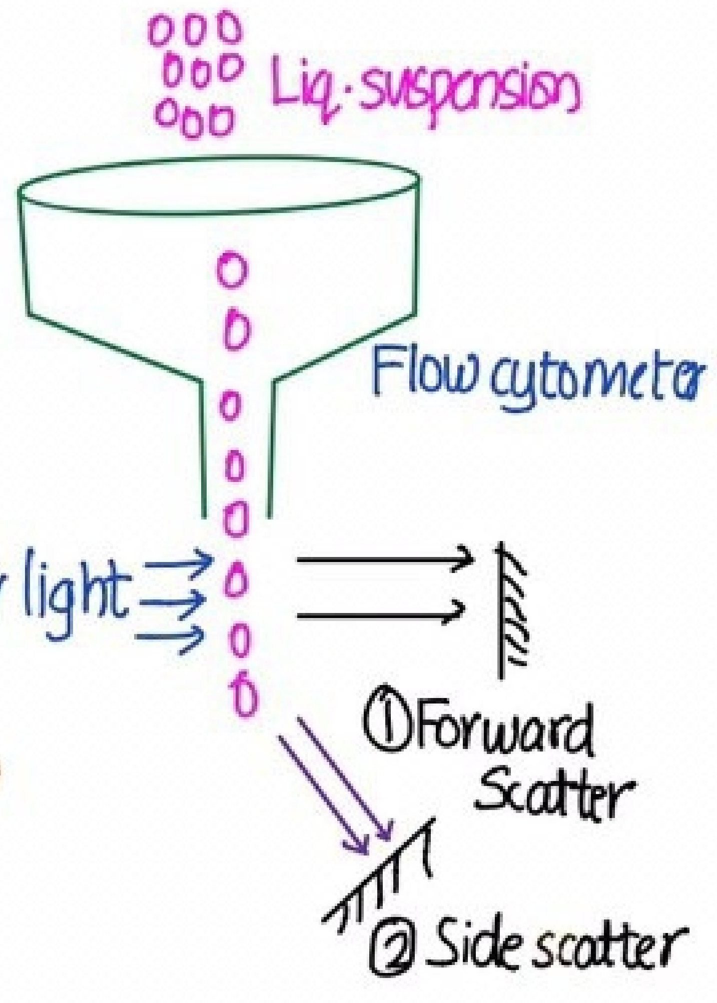
- Confirm the diagnosis

4. Immunophenotyping : Study of CD marker

5. Flow cytometry

- Best for Lymphocytosis ∴ IOC for CLL, PNH
- Principle : Prepare liquid susp. of cells
  ↓
  allowed to pass through Funnel like Flow cytometer
  ↓
  Laser light interaction

Forward Scatter : detection of cell size
Side scatter : detection of cell density
measured by i) Granules of cytoplasm
ii) Membrane size
iii) Vacoule



6. Immunohistochemistry

- Artificial Ab coloured against human tissue Ag

↓ Basis : Intermediate filaments

↑↑↑ Intermediate filament: Hallmark of cell injury

- Intermediate Filaments

1. Cytokeratin in epithelium
   Carcinoma Eg: Poorly diff. carcinoma

2. Vimentin Fibroblast, Adipocytes, Endothelial cell, Mesenchymal
   ∴ marker in Fibrosarcoma
   Liposarcoma
   Melanoma

3. Desmin of skeletal muscle
   ∴ marker in Rhabdomyosarcoma

4. Neuro filament

   ↓ Neuro-endocrine Tumor
   Eg: Carcinoid
   Paraganglioma
   Small cell ca of Lung

   ↓ Neuronal tumor of Brain
   Eg: Ganglioglioma
   Gangliocytoma
   Neurocytoma

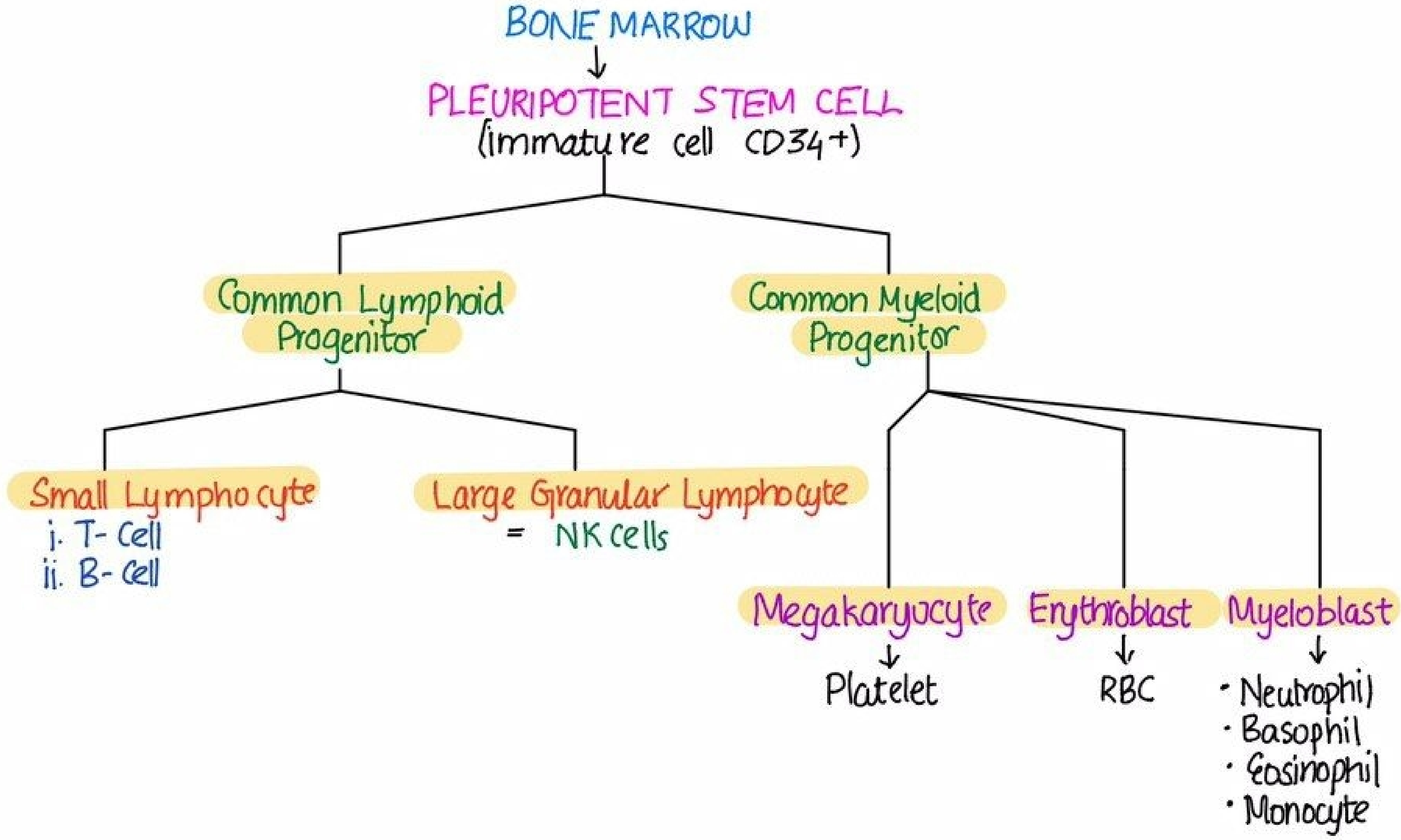
5. GFAP (Glial Fibrillary acidic protein)
   - Marker for Glioma
   Astrocytoma
   Ependymoma
   Oligodendroglioma

ANEMIA

HEMATOPOEISIS

- Starts at Day 10 of embryonic life. (= 3weeks)
- First cell ⟶ RBC ∴ Erythropoeisis starts first
- Sites:

Upto 3 months of intrauterine life : YOLK SAC
1month - birth : LIVER
3month - 7month of intrauterine life : SPLEEN
Birth to adults : BONE-MARROW



Routine Peripheral Smear Stains

Romanowsky-Stain (family of stains)

i. Giemsa
- MC used
- Best stain

ii. Jenner

iii Leishman stain

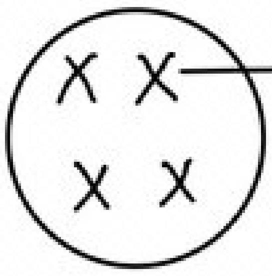
iv. Wright stain

STAGES OF RBC DEVELOPMENT

↓Size

STEM-CELL = Nucleated
↓ EPO = Erythropoeitin
CFU-E
↓
PRO-ERYTHROBLAST (or) PRO-NORMOBLAST : Hb First appears on EM
↓
NORMOBLAST
↓
Early NORMOBLAST : Basophilic Normoblast
↓
Intermediate NORMOBLAST : Polychromatophilic Normoblast : Hb First detected by Routine Stain
↓
Late NORMOBLAST : Orthochromatic Normoblast : Nucleus Removed
↓
Reticulocyte : Present in BM & Peripheral Blood
↓
MATURE RBC = Non-nucleated ← 1-2 days : Maturation time of Retic.

RETICULOCYTES



→ Reticulum like Structures :
↓
These are Ribosomal RNA Proteins

- Non-nucleated
- Reticulocyte size > RBC
- Romanowsky stain can be used for Reticulocyte but not-specific
- SPECIFIC STAIN : Supra Vital Stain (live RBC)
  ↓
  ① BEST : NEW METHYLENE BLUE STAIN
  ② Brilliant - Cresyl Blue
- Reticulocyte present in Peripheral blood
  ↓
  Marker of B·M erythropoeitic activity
- Normal Reticulocyte count = 0.5 - 1.5%

↓sed
* Aplastic Anemia
* Neutritional deficiency
  a) IRON - Iron def. Anemia
  b) Vit B_{12}/Folic acid - Megaloblastic anemia

↑sed
* Hemolytic Anemias
  Eg : G6PD Def.
  Hereditary spherocytosis

i. Reticulocyte Count : % of Reticulocyte in RBC population

ii. Corrected Reticulocyte Count : $\% \text{ of Reticulocyte} \times \frac{\text{Pt's Hematocrit}}{45}$

iii. Reticulocyte Production index : $\frac{\text{Corrected Reticulocyte count}}{\text{Maturation time (P.B)}}$

iv Absolute Reticulocyte count : % of Reticulocyte × RBC counts/mm^3
N : <100×10^9/L

RED BLOOD CELLS

- Normal RBC are Biconcave ∵ of SPECTRIN
  diameter 7-8 μm
  Microcytic : diameter <6 μm
  Macrocytic : diameter >9 μm
- Romanowsky stain the Hb. ∴ Central part of RBC having low Hb ∴ stain pale called as CENTRAL PALLOR
  → 1/3rd of diameter of RBC

  Hypochromic anemia : Central Pallor > ½ of diameter of RBC
- CYTOSKELETAL PROTEINS

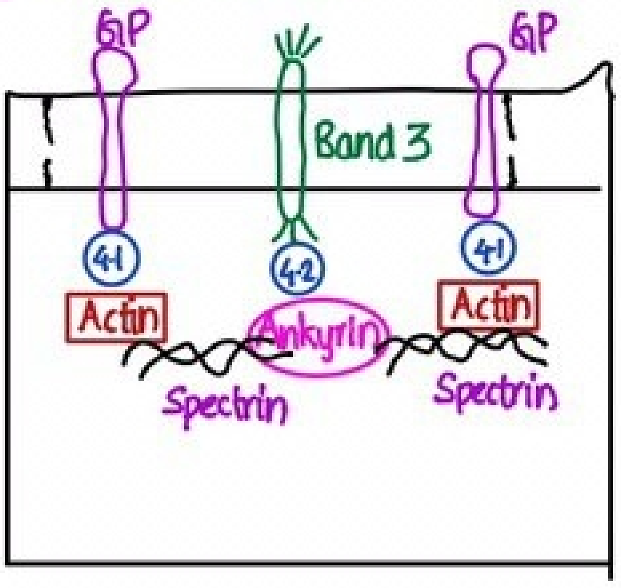
Integral Proteins (I.P)
↓
i. GLYCOPHORIN : Most abundant I.P
A>B>C>D : ↓order of density
↓ Max, ↓ Min
ii. BAND-3 / Anion transport Protein

Peripheral proteins
↓
i. SPECTRIN
Overall M. abundant
ii. ANKYRIN
iii. Protein 4.1
iv. Protein 4.2 / Palladin

function of all these : Provide flexibility to RBC against Hemodynamic stress

- i. Mean Cell Volume : 82-96 FL
  ↓
  - avg volume of 1 RBC
  - Best for size
    · Microcytic : <80 FL Eg : IDA
    · Macrocytic : >100 FL Eg : Megal.

  ii. Mean Cell Hemoglobin : 27-33 pg
  avg Hb in RBC
  ↓
  ↓ in : IDA
  ↑ in : Megaloblastic. A.



iii. Mean Cell Hb Concentration : MCHC : 33-37 gm/dl

↓

- ↓ in IDA
- ↑ in Hereditary Spherocytosis
- N in Megaloblastic Anemia

iv. Red cell Distribution Width : RDW

- For measurment of size variation in RBC
  ↓
  Anisocytosis
- Normal : 11.5 - 14.5
  - Normal : Thalassemia
  - ↑ : IDA / Megaloblastic Anemia

v. Shape variation : Poikilocytosis

ANEMIA

↓ RBC → ↓ Hb & O_2 carrying capacity

Based on mechanism

- **Blood loss**
  - * Acute : Eg Trauma
  - * Chronic : Eg GI Lesions, Gynacological cond.
- **↑ RBC Destruction** (Hemolytic anemia)
  - i. Membrane Defect
    - Hereditary spherocytosis
    - Paroxysmal Nocturnal Hemoglobinuria
  - ii. Enzyme defect
    - G6PD def. Anemia
    - Pyruvate kinase def. Anemia
  - iii. Immune mediated
    - Autoimmune Hemolytic Anemia
  - iv. Hb Defect
    - Qualitative
      - * Sickle Cell Anemia
    - Quantitative
      - * Thalassemias
        - α Thalassemias
        - β Thalassemias
- **↓ RBC Production**
  - i. Nutritional anemia
    - IDA
    - Megaloblastic anemia
    - Sideroblastic anemia
    - Myelopthisic anemia

Based on Morphology (MCV)

- **Microcytic (<80fl)**
  - * IDA
  - * Sideroblastic Anemia
  - * Anemia of chronic disease (ACD)
- **Macrocytic (>100fl)**
  - * Megaloblastic anemia
  - * Hypothyroidism
  - * Alcoholism
- **Normocytic**
  - * Aplastic anemia
  - * ACD (MC)

HEMOLYTIC ANEMIA

- Charachterised
  - * ↑ RBC Destruction
  - * ↑ indirect bilirubin
  - * ↑ EPO Level

[Shortening of RBC Life Span
N - 120 Days
H.A - 10-20 days]

- HEMOLYSIS

Intravascular Hemolysis
ↄ in blood vessel

i. RBC → LDH ↑ S. LDH Level

ii. Heme → ↑ indirect bilirubin

iii. Hb

In P.B
Haptoglobin + Hb
↓
Mo Macro → Liver, → Kidney
⇓
↓↓ Sr. Haptoglobin

Kidney
Hemoglobunuria
↓
In Renal tubule degradation of Hb
↓
Hemosiderin
↓
Hemosideranuria

Eg: Paroxysmal Nocturnal Hemoglobunuria

Extravascular Hemolysis (EVH
by Macrophage - Monocyte System
in SPLEEN
LIVER
Bone Marrow

features of EVH
i. ↑ indirect Bilurubin
ii. Normal to mild decrease in haptoglobin

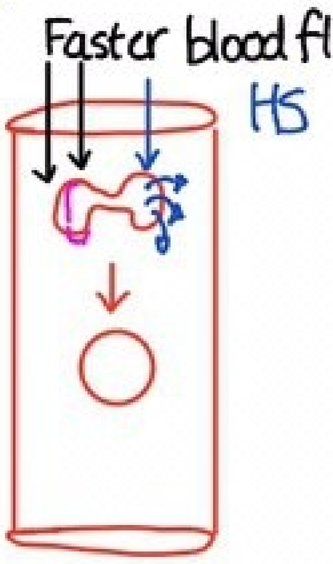
Eg: Hereditary spherocytosis

G6PD def: Both intra & Extra

Sr. Haptoglobin Level ↓
↓
But
it will be appearing to be Normal
} In bile duct obstruction

Hereditary Spherocytosis

- AD ≫ AR
- Membrane disorder : Loss of flexibility
  ↓
  d/t Mutation in Ankyrin
- Severity of H.S is accessed by MUTATION IN SPECTRIN
  ⇓
  Hemolysis
  ↓
  Osmotic Fragility Test
- Pathogenesis :



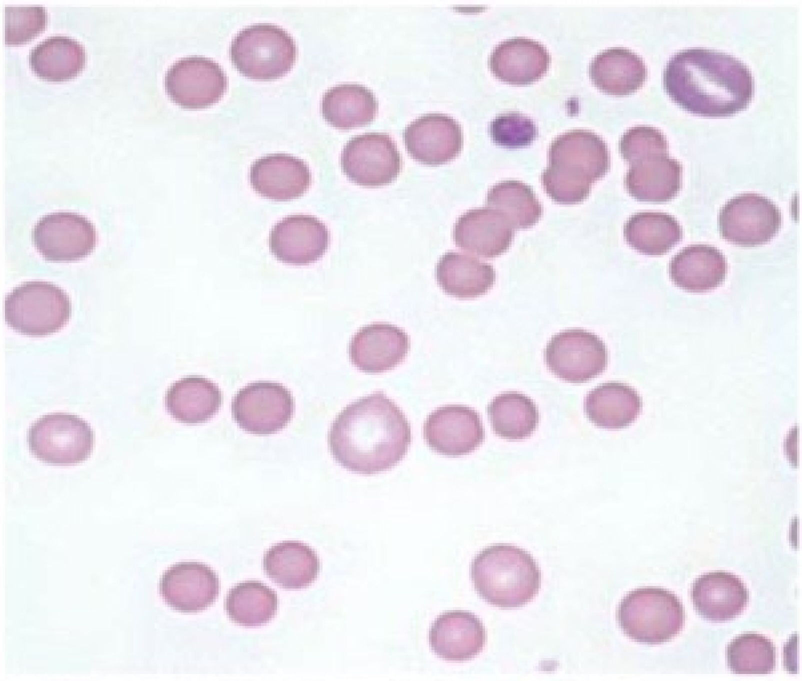
RBC Memb pr. Mutation
↓
No flexibility
↓
RBC Mem. damage
↓
↓ Surface area → Shape to Sphere

* NO CENTRAL PALLOR
* SMALLER THAN RBC
↑

These when reach to Spenic sinusoids
↓
Trapped in sinusoids
↓
Taken up by macrophage system
↓
EXTRA VASCULAR HEMOLYSIS
∴ t/t : SPLENECTOMY
↓
Spherocytes persists in P.B even after splenectomy

Spherocytes are seen in :
- Hereditary spherocytosis
- PNH
- G6PD - Def Anemia
- AIHA (MC seen in)

- Clinical Feature : i. ↑ indirect bilirubin
↓
Jaundice
ii. Pigmented Gallstone
iii. Mild - Moderate Anemia
} TRIAD



HEREDITARY SPHEROCYTOSIS
RBC with smaller size in comparison to normal RBCs, no central pallor. Spherocytosis is most commonly seen in Auto-immune hemolytic anemia.

CRISIS : a) Hemolytic Crisis
a/w infection of EBV
b) Aplastic crisis : Transient for 5-7 days
caused by Parvo Virus B19 inf.
↳ ↑ affinity for Erythroid progenitor
↓
all stem cells affected
↓
∴ PANCYTOPENIA / APLASTIC

- LAB DIAGNOSIS : • ↑ MCHC
• ↑ Reticulocyte (known case of Aplastic Crisis : ↓)

Screening test : i. Osmotic Fragility Test / Pink's OFT
- ↑ in HS
Ⓝ RBC $\xrightarrow{\text{isotonic}}$ 0.9% of NaCl
↓
Hemolysis
↳ Starts at 0.5% NaCl
↳ Completed by 0.3% NaCl

Hemolysis : >0.5% NaCl ⇒ ↑↑ OF
Hemolysis Not completed even at 0.3% ⇒ ↓↓ OF
↓
in Thalassemia

ii. Osmotic Gradient Ektacytometry
- Better
- Best for in New born baby

Confirmation : Flow cytometry
↓
Eosin-5-Maleimide test (EMA)

G6PD - DEFICIENCY ANEMIA

- X-linked Recessive
- ∴ M >> F
- Etiology :

i. Infections ii. Drugs iii. food

Primaquine >> Dapsone (MC) Fava-beans [FAVISM]

- Pathogenesis :

⇓
↑ oxidant stress
↓
Denaturation & Misfolding of Protein
↓
RBC Hemolysis
(both IVH + EVH

① FR produced will
Denature Hb
(Denatured Globin)
↓
HEINZ Bodies

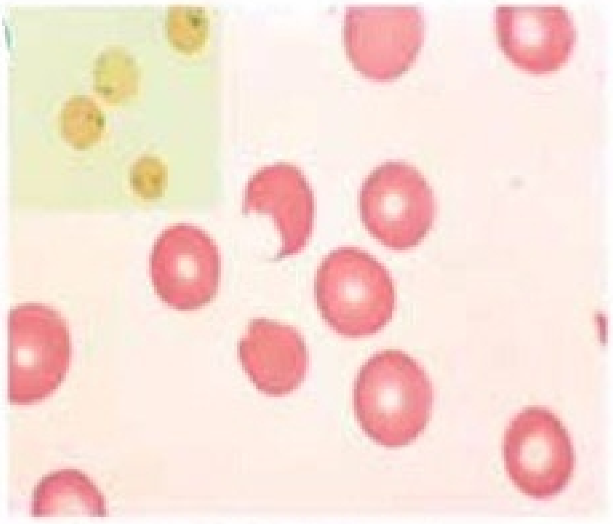
② BITE CELLS/DEGMACYTES

: Most charachteri. Finding

These are due to
Denatured Hb
not macrophage eating

Normal HMP Pathway
↓
G6PD produced
↓
NADP ⟶ NADPH
↓
Glutathione → Reduced Glutathione

Inf/D/Food
↓
FR production ⟶ Neutralise FR⊖
∴ RBC Survived



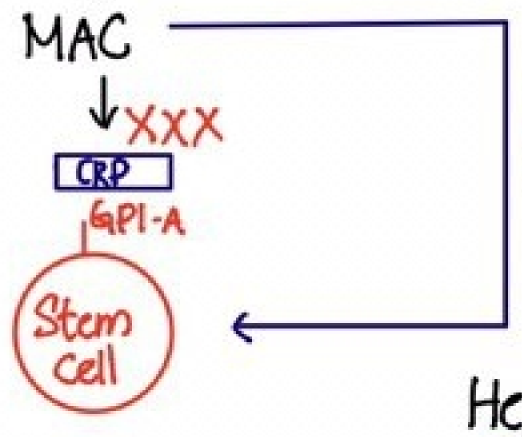
BITE CELLS (=DEGMACYTES)
RBCs with appearance of bite due to unstained denatured haemoglobin within the cytoplasm.
(In satellite) RBC with precipitates of denatured globin (Heinz bodies) detected by supravital staining by brilliant cresyl blue stain.

Heinz Bodies can never be stained by Romanowsky Stain
↓
Supra Vital Stain : CRYSTAL VIOLET

- Clinical Features : Episodic Hemolysis
Features of chronic hemolysis absent.
i.e Spleenomegaly
Chole lithiasis

Paroxysmal Nocturnal Hemoglobinuria

- Misnomer as both Paroxysmal & Nocturnal both in only 25% patients
- Acquired Somatic Mutation in PIGA Gene (Most important Gene)
  ↳ Phosphatidyl Inositol Glycosyl-A Gene
  Help in GPI - Anchor Protein
  present on stem cell
  anchor Complement Regulatory Protein (CRP)
    → CD59 (m.imp) : Membrane Inhibition of Reactive Lysis (MIRL)
    → CD55 : Decay accelerating Factor → DAF
    → C8 Binding Protein
- Pathogenesis : Acidic pH [Night, Stress]
  ↓
  Complement Pathway
  ↓
  MAC



in PNH Lysis ⟹ * PANCYTOPENIA
* HEMOLYTIC ANEMIA
* THROMBOSIS (GI)
↓
Hepatic Vein Thrombosis : MCC of Death
Bud chiari Syndrome

- Form of IVH
- Screening test : i. Ham's Test (mildā) ii. Sucrose Lysis test (acidic sugur)
  iii. GEL-CARD TEST
- Confirmation : Flow Cytometry

# PNH → Aplastic Anemia (transform)
PNH ↓ MDS (transform)
PNH → Acute Leukemia
Aplastic Anemia ↓ Acute Leukemia
MDS → Acute Leukemia

Preleukemic Condition
* PNH
* Aplastic
* Acute leukemia

# Sample for urine Routine microscop
Early morning, 1st void, Mid-stream

Autoimmune Hemolytic Anemia / Immune Hemolytic Anemia

- Antibodies are formed against RBC & Hemolysis
- F > M, 20-50 yrs.
-

AIHA
- Warm : MC
- Cold ; Ab $\xrightarrow[4°C]{}$ RBC

* Ab $\xrightarrow[37°C]{}$ RBC

Warm : MC

$\ast$ Ab $\xrightarrow[37°C]{\Downarrow}$ RBC

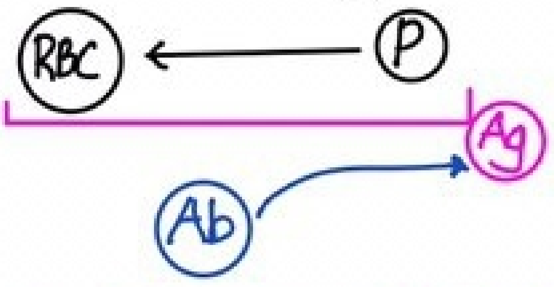
$\ast$ by IgG Abs

$\ast$ a/w
- Chronic Lymphocytic Leukemia
- Autoimmune disorders: SLE (MC)
- Drugs

Antigenic Drug

Eg: Pencillin

When Pencillin getting deposited to RBC This entire complex behave as Ag



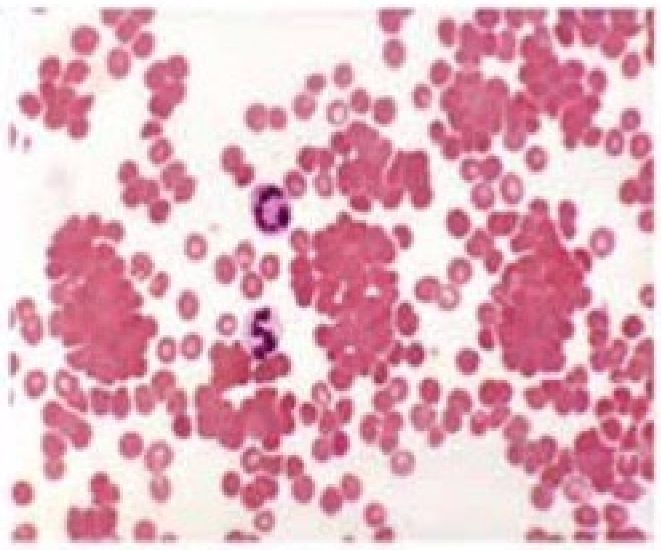
Tolerance breaking Drug

α-methyl DOPA

↓ induce

Auto Ab

↳ RBC



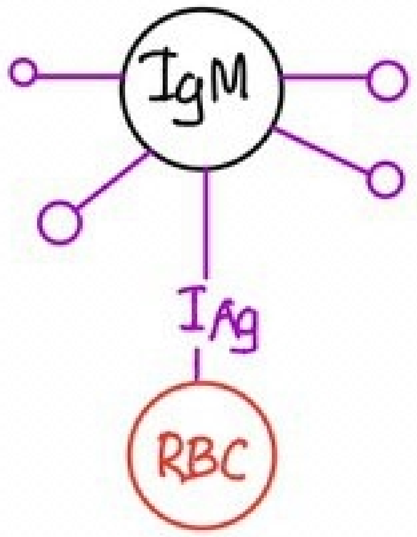
COLD TYPE AIHA

Peripheral smear showing autoagglutination (Clumping of erythrocytes) where outlines of individual cells may not be visible. It is associated with Antigen-antibody reactions and these Aggregates will not disperse with saline.

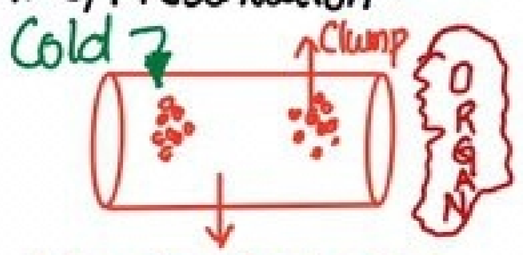
Cold ; Ab $\xrightarrow[4°C]{\Downarrow}$ RBC

Cold Agglutinin

$\ast$ IgM type Ab



$\ast$ C/Presentation :



↓

Vascular obstruction

↓

Ischaemia

↓

Raynaud's Syndrome

(Pallor ⟶ Cyanosis ⟶ Reddness)

$\ast$ Peripheral Smear

i. Agglutination or clumps

Eg: Mycoplasma inf

Viral inf of HIV

Cold Hemolysin

$\ast$ IgG type Ab

↓

also known as Donnath-Landsteiner Ab

↓

in PCH [Paroxysmal Cold Hemoglobinuria]

IgG ⟶ P-Ag-(RBC)

↓

Complement

↓

MAC

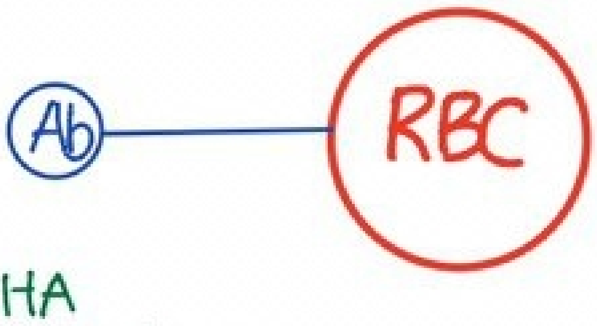
↓

Lysis of RBC

$\ast$ MCC : Viral infection

- Confirmation of AIHA : Coombs Test

Direct



- # AIHA
- # Drug - HA
- # Hemolytic Disease of Newborn (HDN)
- # transfusion Reaction

CT +: Immunogenic Thrombocytemic Purpura (ITP)

CT − : • HUS • TTP

Indirect

Ab: Serum

- # HDN in mothers sample (as Ab in serum)
- # Compatibility testing
- # Unexpected Ab in Rare Blood groups

↓

Kelly, Duff, Bombay blood group.

for more notes join our telegram channel,"latest neet pg notes 2020" or join via link "t. me/latestpgnotes"

Hemoglobinopathy

- Ontogeny of Hb

① Embryonic Hb (8 weeks of IU Life) →
  - i. Gower I → Zeta$_2$ (ζ_2) Epsilon$_2$ (ε_2)
  - ii. Gower II → $\alpha_2\ \varepsilon_2$
  - iii. Portland I → $\zeta_2\ \gamma_2$
  - iv. Portland II → $\zeta_2\ \beta_2$

↓

② Fetal Hb : $\alpha_2\ \gamma_2$

↓

③ Adult Hb: $\alpha_2\ \beta_2$

In any normal adult :
- HbA : 96%
- HbF : <2% ⇒ 6 months of neonatal life.
- HbA$_2$: upto 3.5%

- Hemoglobinopathies

Qualitative

i. Sickle Cell Anemia

$\alpha_2\ \beta_2$ → 6 → Valine replaced Glutamic acid

→ MC Genetic Lesion:
Point Mutation (Missense)
[Partially acceptable mutation]

Quantitative

i. α Thalassemia : ↓ α chain : Deletion

ii. β Thalassemia : ↓ β chain

→ Point mutation (Non-sense)

Sickle Cell Anemia

- AR ; Hb in Homozygous HbSS Disease
  Hb in Heterozygous HbSA Carrier/trait
- Pediatric patient, Africo-american origin

Pathogenesis : Point mutation
↓
β chain 6th position
↓
Glutamic acid → Valine

Glutamic acid	Valine
(Polar aa)	(Nonpolar aa)
- Water soluble	- Insoluble
- Negatively charged	- Neutral

∴ Solubility altered

HbS —S #sticky-site present in both oxygenated & deoxygenated state

↓

HYPOXIA

#complementary site ↓

—S + C —HbS —S+C →

Polymerisation of Hbs

↓

Needle crystals

↓

distortion of RBC Shape

Sickle cells / Drepanocytes

- Clinical feature :

① Vaso-occlusive crisis

$\downarrow O_2$

↓

↑ expression of Adhesion molecule

↓

Thrombosis

↓

ISCHAEMIA

↓

INFARCTION & FIBROSIS

Eg: i. Hand-foot Syndrome
  - Pediatric
  - Painful extremities

↓

Dactylitis

d/d: Acute osteomyelitis

ii. Fish mouth vertebrae

iii. SCA → Osteomyelitis is MC caused by → Salmonella (>80%/>50%)

iv. Auto splenectomy

Ischaemia/infarction

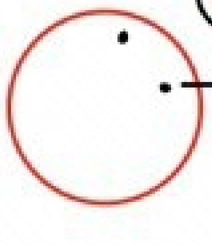
↓

fibrotic band in spleen

↓

ineffective erythropoeisis

PB



→Nu. Remenents in PB

HOWELL-JELLY BODIES (Consist of DNA) →
i. SCA
ii. Sx-Splenectomy
iii. Thalassemias
iv. Hered. Spheroc.
v. Megalo. Anemia.

② Aplastic crisis
- caused by parvo virus B19 infection
- Transient (5-7days)

③ Sequestration crisis
- most dangerous & life threatning crisis
- large amount RBC

↓

dumped ɔ̄ in spleen

↓

Painful: Acute Spleenomegaly

⇓

Hypovolemic Shock
- Die within 4hrs
- Pediatric patient
- Treatment: Blood Transfusion considered as Medical Emergency

#Gamma-Gandy Bodies
· Sign of conjestive spleenomegaly
· Composed of : Fe
  Ca
  Fibrotic areas of spleen
· Seen in : CML, Liver Cirrhosis, SCA

- Factors affecting sickling
  - i. Most important Factor : HbS concentration
  - ii. Sickle cell carrier

↓

HbS A → No sickling

↓ ↓ ↓

40% 60% ∵ HbA inhibits polymerisation of HbS

[as Hb A *no sticky site
*Receptor for S' end present]

# Other Hb

HbA
Hb F } ⇒ ⊖ polymerisation → ↓↓ sickling

Q HbC [Hb SC] : ↑ incidence of • Proliferative Retinopathy
• Bone infarction

HbC → Remove Na^+ H_2O
HbS ↑↑ → Sickling

iii. Hypoxia → ↓ O_2 ↑ CO_2 → H_2CO_3 ⇒ H^+ → Acidic pH

Promotes sickling

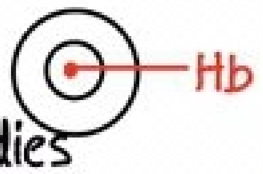
iv. ↑ MCHC : Dehydration → ↑ HbS Concentration
v. SCA + Thalassemia : Hb S ↓ (as chain synthesis ↓)

↓

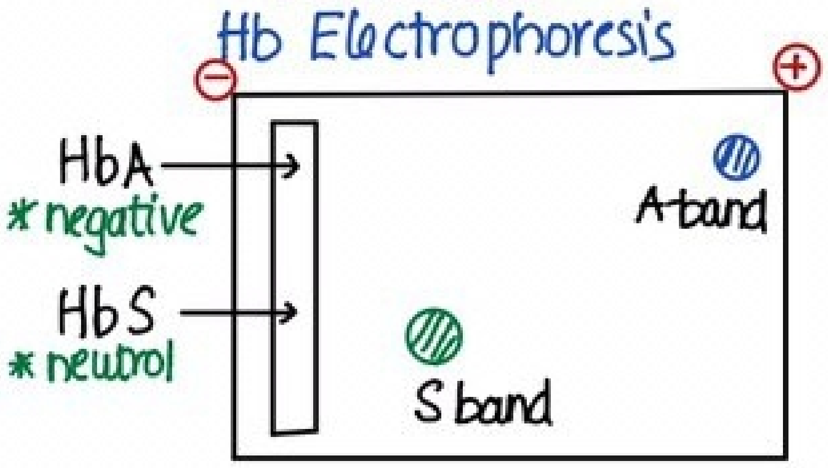
∴ Sickling decreases

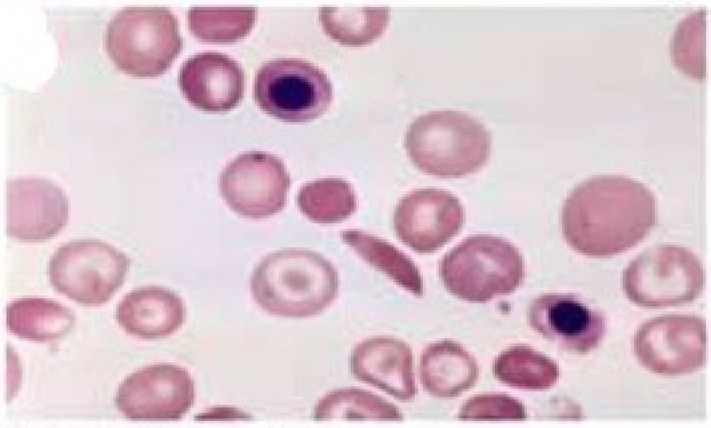
# HbF persist upto 6 months : ∴ no sickling upto 6-9 months

- Diagnosis : • Peripheral smear : i. Sickle cell
  ii. Target cells
  iii. Howell - Jolly Bodies

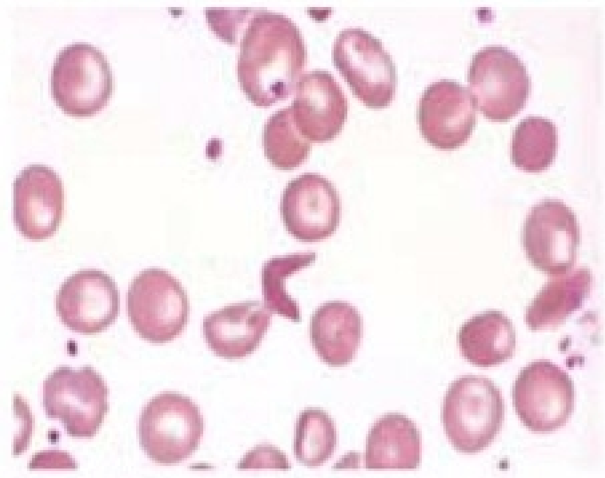


- Screening :
  # Sodium Metabisulphite
  # Sodium Dithionite test
- Confirmation :
  Hb Electrophoresis





SICKLE CELL ANEMIA
Peripheral smear showing anisocytosis, Poikilocytosis, sickle cells, target cells, nucleated RBC, schistocytes, and Howell-Jolly bodies.



SICKLE CELL ANEMIA
Peripheral smear showing anisocytosis, Poikilocytosis, sickle cells, target cells,

# investigation of choice for any hemoglobinopathy
High Performance liquid Chromatography - HPLC

if 2 bands : → HbSA : Carrier
if 1 band : → HbS : SCA

Thallasemia

- AR ; MC Hemoglobinopathy in world & india

α- Thallasemia

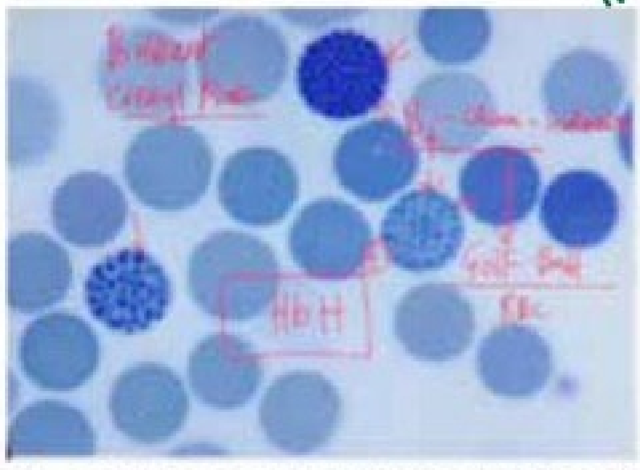
- Mutation in α gene - Chr:16
- α Globin chain $\xrightarrow{\text{coded by}}$ $\overbrace{\alpha\alpha \mid \alpha\alpha}^{\text{gene}}$

⇒ MC genetic change : Deletion

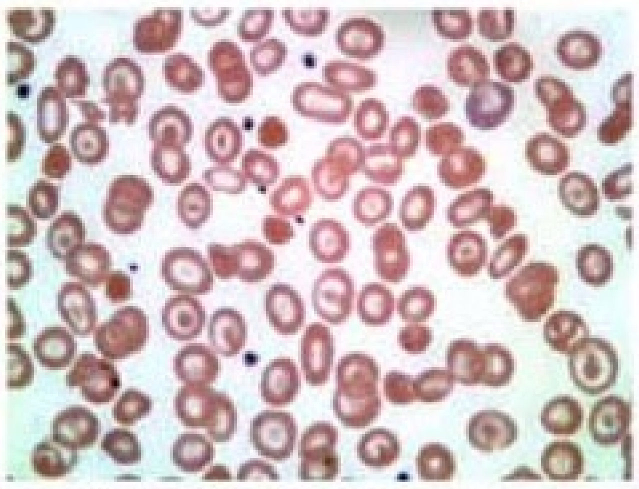
① 1α gene deletion → α Thallasemia Carrier
② 2α gene deletion → α Thallasemia trait
③ 3α gene deletion → HbH disorder
Clinical resemblance : β-Thallasemia intermedia.
④ All 4α gene deletion → HYDROPS FETALIS (non-immunogenic)
Hb-BARTS

- Diagnosis : i. Peripheral Smear
  - Poikilocytosis : variable shape & size RBC
  - Microcytic & Hypochromic Anemia
  - Target Cell

HbH : Tetramers of β chain
↓
aggregates
↓
deposition ∃ in RBC
↓
GOLF-BALL RBC



ALPHA -THALASSEMIA (HBH)WITH BRILLIANT CRESYL BLUE STAIN.
Three cells have Haemoglobin H inclusions giving the cells a golf ball like appearance.



ALPHA -THALASSEMIA (HBH)
Peripheral smear showing microcytic, hypochromic RBCs with target cells, Poikilocytosis.

β- Thallasemia

- β chain ↓ ⇒ β-gene Chromosome 11
- Molecular pathogenesis : Non-sense Point Mutation (MC)

SPLICING SITE Mutation
defective mRNA processing
↓
Abnormal mRNA
Nu. Degradation
- Partial
  * Reduced β chain Synthesis
  ↓ β^+ Thal.
- Complete
  * β-chain absent
  ↓ β^0 Thal.

CHAIN TERMINATING Mutation
No translation (d/t Nonsense/ Frameshift mut)
↓
No β-chain
↓
β^0 Thal.

CHAIN PROMOTER Mutation
↓ Transcription of β-chain
↓
β^+ Thal.

⇒ ↓ / Absent β-chain

→ Microcytic Hypochromic Anemia

→ M.important: ↑ α chain synthesis
↓
Abnormal aggregates
↓
destroy cell-membrane of
→ Immature precusor In B.M
→ Mature RBC In P.B

} Anemia

- Q. 21 yr F ; Hb = 5gm%. , Hepatospleenomegaly, recieved only 1 unit of Blood transfusion
  a) β-Thal major
  b) β-Thal interme
  c) β-Thal Trait
  ✓d) AIHA : Auto Ab → RBC   Sever Hemolysis → Hb↓ ↓ Blood transfusion

I. β-Thal. Major

- aka Cooley's Anemia
- aka Mediterranean Anemia
- Pediatric patient (6-9months)
  ↓
  Hb → low (<3gm%.)
  ↓
  ∴ Blood transfusion (Repeated)
  ↓
  Iron overload
  ↓ production F.R
  Congestive Heart Failure
  [d/t dialated cardiomyopathy more than Restrictive C.M]
  MCC of Death : CHF
- Survive 10-20yrs
- aka Transfusion depend. Anemia
- Diagnosis : • Hb Electrophoresis
  • IOC : HPLC
- ↑ Hb F : >30-90%.

II β-Thal. Intermedia

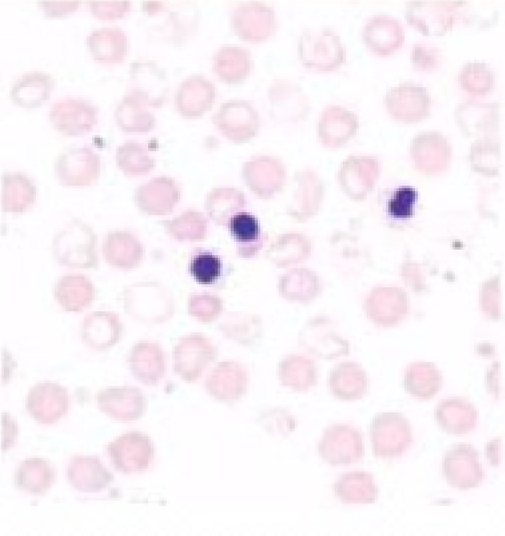
- Pediatric patient
- Hb : >7%.
- initially that is pediatric age group
  : Occasional blood transfusion
- Adults : Multiple Blood transfusion
  aka Transfusion depend. Anemia
- Diagnosis : • Hb Electrophoresis
  • IOC : HPLC
- ↑ Hb F : 10-30%.

III. β-Thal. Trait / minor

- Pediatric / Adults
- Asymptomatic Hb : 9-12gm%.
- No h/o Blood transfusion
- Diagnosis : HPLC
  HbF ↑ *non-diagnostic (1-2%)
  Hb A_2 ↑ *diagnostic dx : 4-8%

Peripheral smear

i. Poikilocytosis
ii. Microcytic hypochromic Anemia
iii. Anisocytosis : Size variation
iv. Target cell (Most-Charochteristic)
v. Basophilic stippling
vi. Nucleated RBC
vii. Howell Jolly bodies

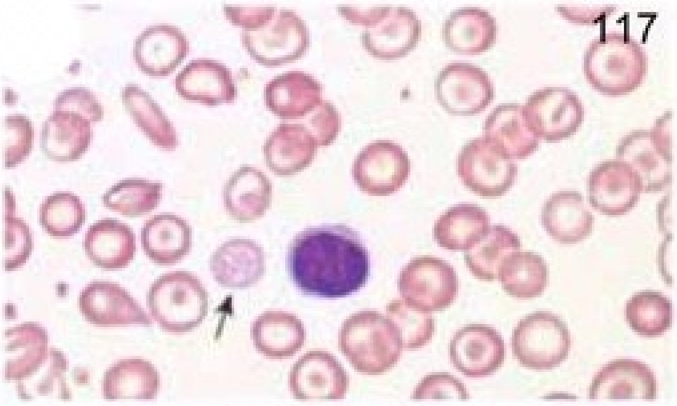


BETA-THALASSEMIA MAJOR
Peripheral smear showing marked variation in size (anisocytosis) and shape (Poikilocytosis), numerous nucleated erythrocytes, microcytes, hypochromia, target cells, basophilic stippling, tear drop cells, schistocytes.

Thal. Minor
↓
Microcytic Hypochromic anemia
d/d : IDA

1. RDW
   - N = 11.5 - 14.5 ; in Thal. minor
   - ↑ RDW in IDA
2. Mentzer's Index

$$\frac{MCV}{RBC\ count} = \underset{\text{Thallassemia}}{\underset{\downarrow}{<13}} \qquad \underset{\text{IDA}}{\underset{\downarrow}{\geq 13}}$$

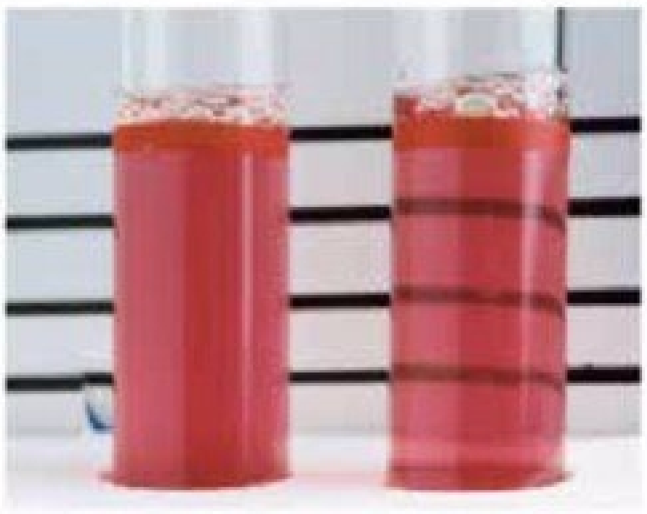


BETA -THALASSEMIA MINOR
Peripheral smear showing microcytic, hypochromic RBCs with target cells, Poikilocytosis, and basophilic stippling (arrow). Presence of basophilic stippling is common in thalassemia minor but not in iron deficiency anemia.

Screening of Thallasemia
- MC Test : NESTROF - Test

Naked
Eye
Single
Tube
RBC
Osmotic Fragility

- Add 0.3 % NaCl
  if hemolysis complete : Ⓝ RBC
  in Thal. stable RBC membrane present



NESTROF TEST (NAKED EYE SINGLE TUBE RBC OSMOTIC FRAGILITY TEST)
It is used for thalassemia screening. Interpretation of test :
a) Lines seen --NORMAL.
b) No lines (because thalassemia has stable RBC membranes) -----Thalassemia patient

Iron Deficiency Anemia

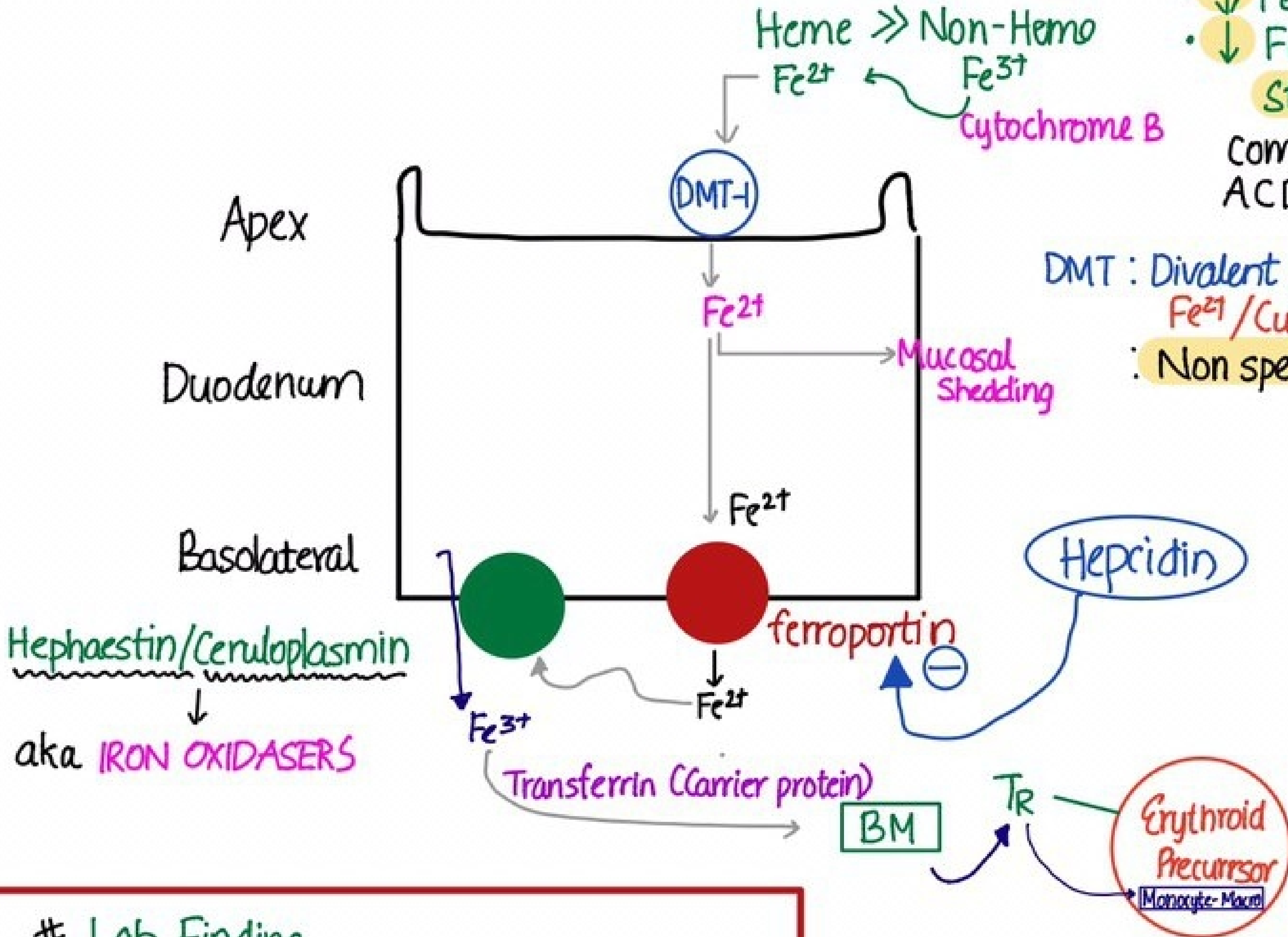
- MC Nutritional Deficiency anemia
- C/F :
  - MC Presentation : Fatigue & Irritability
  - Latent Iron Defiency Anemia : MC Lab presentation in World & India
    ⇓ i.e
    Iron deficiency without anemia
    i.e ↓ iron stores, but Ⓝ Hb level
  - * Pediatric patient ⟶ "PICA"
    (↑ tendency to eat non-food stuffs)
  - * Plummer Vinson - Syndrome :
    ↳ a/w i. Microcytic hypochromic anemia
    ii. Atrophic glossitis
    iii. Eosophageal web
- IRON METABOLISM :
  - * Absorption : Fe^{2+} form
    M.C Site : S.I (proximal duodenum)

Factors ↑ Fe^{2+} Absorption	Factors ↓ Fe^{2+} Absorption	
· Acidic pH	· Alkaline pH	· Milk / EDTA / Ca^{2+}
· Citric acid	· Phytates	· Tetracycline
· Ascorbic acid = Vit C	· Phosphates	
	· Tannates	

* Storage form of Iron : Fe^{3+} in RE-System [Ferritin]

Master regulator of Fe-absorption : HEPCIDIN

- ↓ Fe absorption
- ↓ Fe Mobilisation from storage site (Most common mechanism for ACD)



DMT : Divalent Metal Transporter

$Fe^{2+}/Cu^{2+}/Pb^{2+}/Cd^{2+}$

: Non specific protein

Ferritin

↓some

Sr. Ferritin

(Marker of Storage Iron)

Lab Finding

i. Earliest lab finding, Most sensitive } ↓ Ferritin

↓

ii. ↑ Transferrin

↓

iii. ↑ TIBC (Total iron binding Capacity)

(Ⓝ = 300-400 μg/dl)

[IDA : >400
ACD : <300]

iv. ↓ % saturation of transferin.

IDA <15%.

vi. Serum Iron ↓

vii. Hepcidin ↓

IDA c̄ Chronic inflammation

↓

↑ Sr. Ferrittin

(as it's +ve Acute. Phase Responce protein)

∴ Sr. Ferritin is of no use

∴ IDA c̄ inflammation

i. BM biopsy c̄ Pearl's Prussian Blue stain (Gold standard)

ii. ↑ S. Transferin Receptor

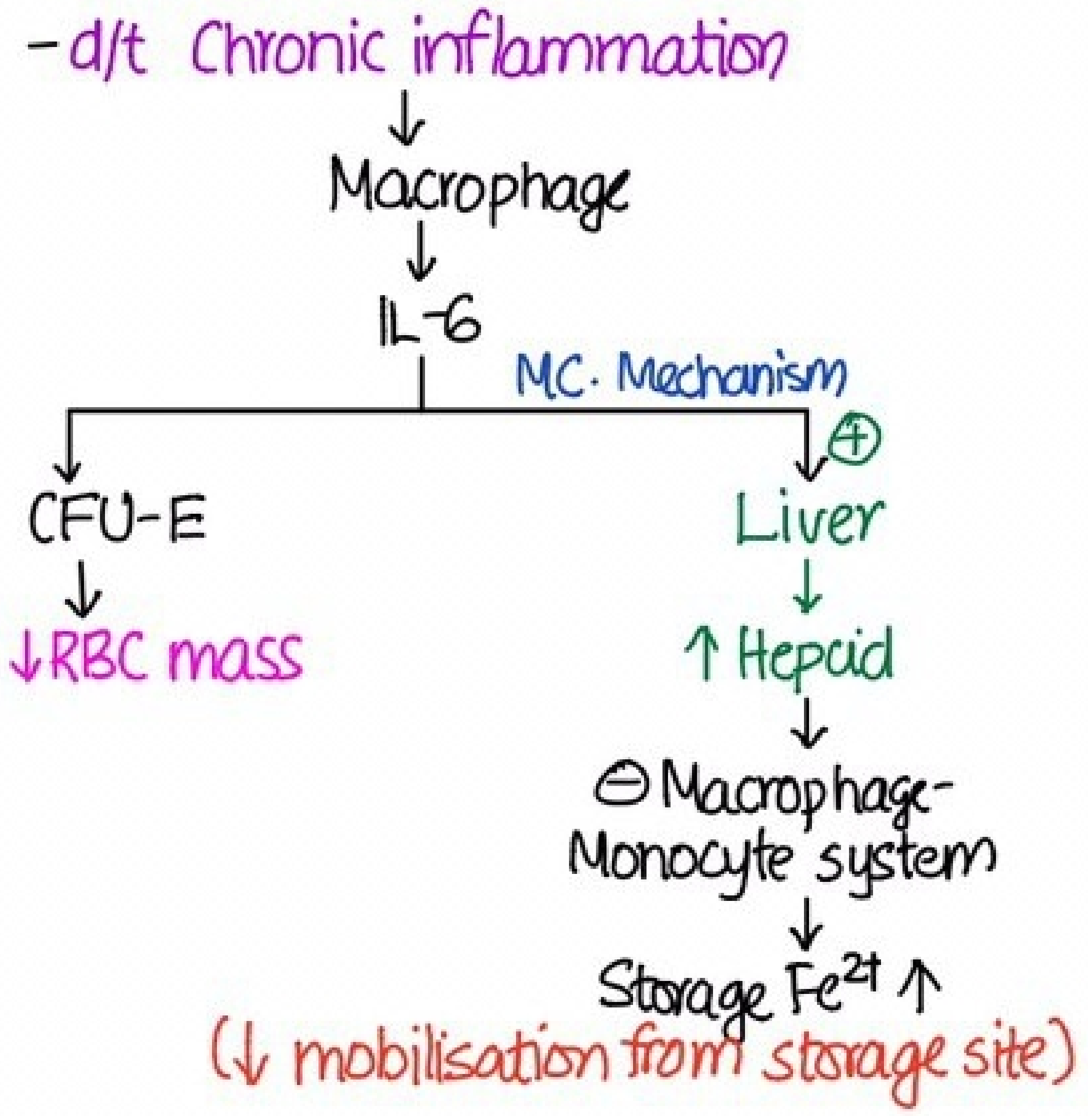
Peripheral Smear

i. Microcytic Hypochromic

ii. Target cells

Anemia of Chronic Disease (ACD)

- d/t Chronic inflammation



- Lab findings :
  - i. ↑ S. Ferritin
  - ii. ↓ Transfferin
  - iii. ↓ TIBC
  - iv. ↓ % transferin saturation
    - in IDA ↓ is milder
    - ACD ↓ is severe
  - v. ↑ Hepcidin
- Peripheral smear
  - i. Microcytic Hypochromic
  - ii. Normocytic Normochromic (MC)
- Condition with ACD
  - Rheumatoid arthris
  - A.I dis like SLE

Megaloblastic Anemia

- due to
  - i. pernicious anemia
  - ii. Vit B_{12} ↓ : MC Cause
  - iii. Folic acid ↓

* Vit B_{12} Metabolism
- Non vegetarian food : Richest source
- Vegetarian : Poor B_{12} def.

⇒ Dietary Vit B_{12} → Vit B12 + Haptocorrin (Salivary Gland)

↓

Stomach : Fundus (Parietal cell)

↓

IF (Intrinsic Factor of castle)

↓

Duodenum : Pancreatic Proteases
Haptocorrin seperated from Vit B_{12}.

↓ +IF

TERMINAL ILEUM
[IF_R (CUBULIN) + IF]

↓

Ileal epithelium

Trans cobalamin-II + Vit B_{12}/IF

↓

Other tissue

Pernicious Anemia	Vit B_{12} Deficiency	Folic Acid Deficiency
- Auto immune disorder Auto Ab → Parietal epi. ↓ i. Vit B_{12} def ii. Atrophic gastritis ↓ Gastric Adenocarcinoma (MC : Fundus) iii. Gastric atrophy iv. Peripheral neuropathy	- Stomatitis - Glossitis - Gastric atrophy - Peripheral Neuropathy	i. No peripheral neuropathy ii. No gastric atrophy # Folate transporter gene mutation (In Ch 21q)

Methy Malonyl CoA $\xrightarrow{\text{Vit B12}}$ Succinyl CoA

↓

* Help in Myelin Synthesis

∴ Absence of Vit B12

Methyl malonyl CoA → • Methyl Malonic Acid
+
• Propionic acid
(These are toxic)
Cause damage of myelin

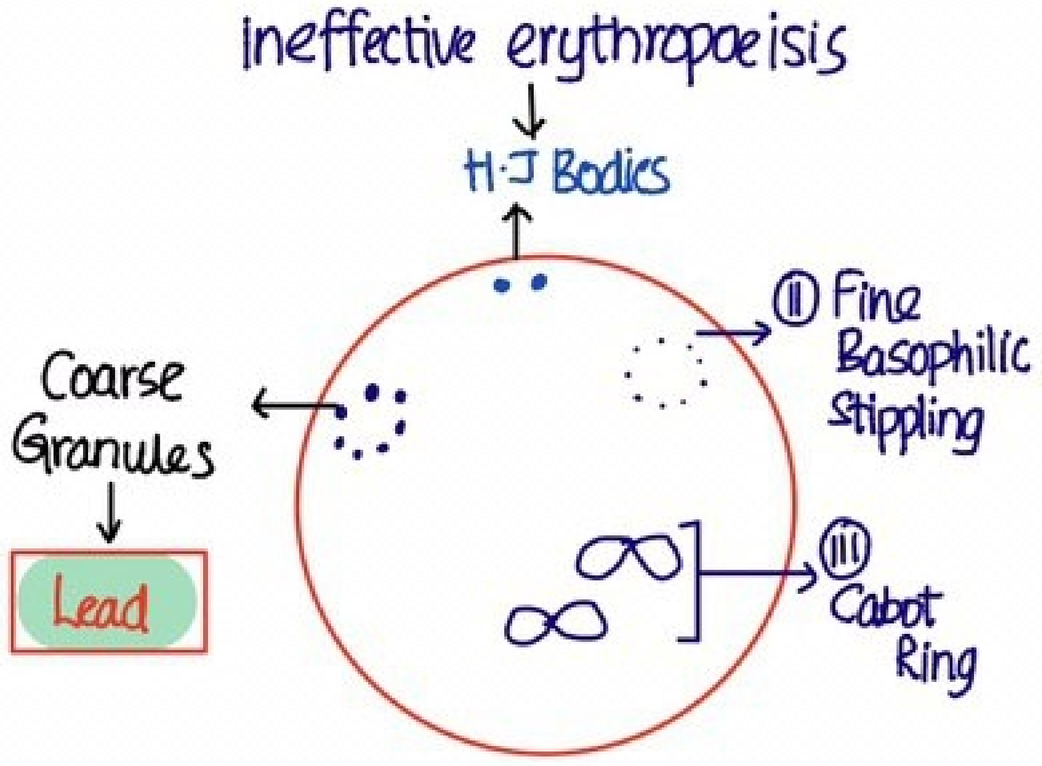
POSTERO-LATERAL TRACT/DORSO-LATERAL more effected ← Cause damage of myelin

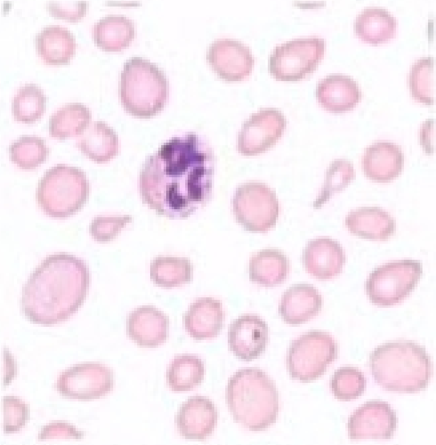
⇓

* Sub acute combined Degeneration of Spinal cord.
* Peripheral neuropathy
* loss of pain & vibration
* Hyper reflexia

Peripheral Smear :

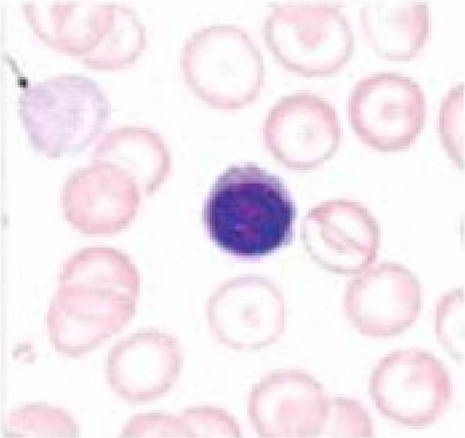
Charachteristic triad
- i. Earliest finding : Macro-ovalocytosis
  when MCV > 100 fl (or)
  diameter of RBC > 9 μm
- ii. HYPERSEGMENTED Neutrophil
  : Most specific
  : Ⓝ Neutrophil : 3-5 lobes.
  : i. > 5 nucleor lobes
  ii. > 5% of Neutrophil
  ≥ > 5 lobes
- iii. Howell-Jolly bodies
- iv. MCHC : Normal





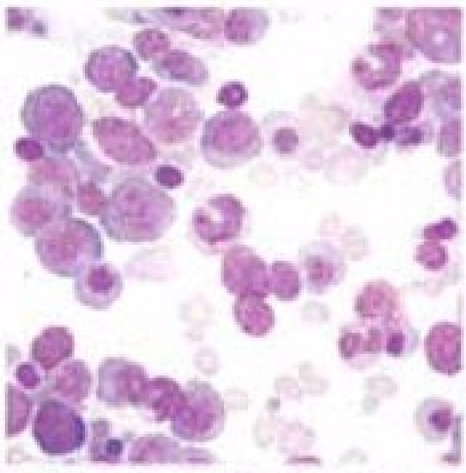
MEGALOBLASTIC ANEMIA

Peripheral smear showing Pancytopenia, hypersegmentation of neutrophils, oval macrocytes, Howell-Jolly bodies, nucleated erythrocytes, basophilic stippling, schistocytes, spherocytes, tear drop cells, target cells, and giant platelets.



MEGALOBLASTIC ANEMIA (BASOPHILIC STIPPLING AND NUCLEATED RBC)

Peripheral smear showing oval macrocytes, nucleated erythrocytes, basophilic stippling,and target cells.



MEGALOBLASTIC ANEMIA (BM)

Bone Marrow showing Hypercellular, asynchrony (trilineage) with nuclear maturation lagging behind cytoplasmic maturation, sieve like nuclear chromatin, giant bands, giant metamyelocytes, hypersegmented neutrophils.

BM Biopsy / Aspirate

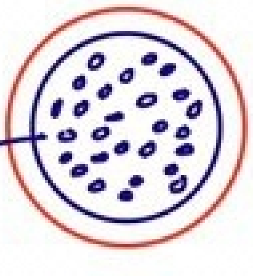
* BEST SITE for infants : Antero medial aspect of TIBIAL Head
for Children & adults : Post. Ileac Crest

- Ⓝ Myeloid : Erythroid Ratio = 3 : 1 (M:E Ratio)
- In Megaloblastic Anemia Reversal of M:E Ratio

∵ Megaloblastic cells
↓ passing through small vessel
Difficult
↓
Hemolysis : ↑ Nu RBC, Jaundice, Spleenomegaly
↓
Erythroid Hyperplasia

Reticulocyte count : Decreased (Due to Vit B12 ↓)

i. Nucleo-cytoplasmic Asynchrony
ii. Sieve like Nuclear Chromatin



Sideroblastic Anemia

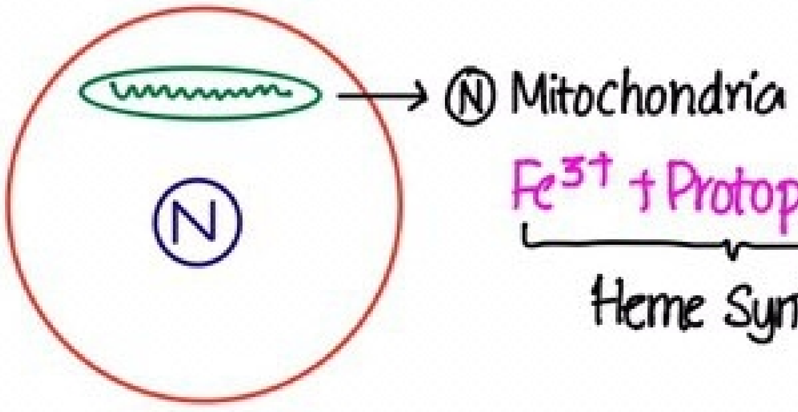
⇒ Production of Sideroblast / Ringed Sideroblast are produced.
↓
These are produced instead of Mature Healthy RBC

⇒ Etiopathogenesis : ETIOLOGY

Hereditary
- X-linked Recessive > AR
(MC)

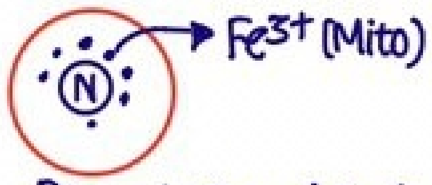
Acquired
- Drugs :
  - Isoniazid
  - Alcohol
  - Pyridoxine def.
  - Chloramphenicol
- Lead toxicity
- Seen in Hematological condition
  - MDS
  - Myeloma
- Auto immune disorders • SLE
- Misc. • Iron overload disorder
  - Porphyria

⇒ Pathogenesis :



$\underbrace{Fe^{3+} + \text{Protoporphyrin}}_{\text{Heme Synthesis}}$

In Sideroblast
↓
Fe^{3+} deposited c̄ in Mitochondria

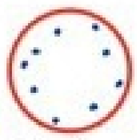


Ringed Sideroblast
(not mature in to Ⓝ RBC)
↓
Anemia
Iron overload

Sideroblast are found in Ⓝ BM : 20-40%

Peripheral Smear :

- * Dimorphic RBC
  [Microcytic Hypochromic
  +
  Macrocytic Anemia]
- * Target Cells
- * Basophilic Stippling →



- * Papenheimer bodies (Non-Heme Iron)
  in Siderocytes ↘

CBC : i. RDW : Increased
ii. S. Iron : High
iii. S. Ferritin : High
iv. S. Transferring : ↓
v. TIBC : ↓
vi. % Saturation of transferrin : High

* Iron overload
↓
CHF/Dialated Cardiomyopathy
MCC of death.

Aplastic Anemia

- BM Failure
- Chronic Primary Hematopoeitic failure c̄ Pancytopenia
- Etiopathogenesis : ETIOLOGY :

i. Drugs (MCC) : Alkylating drugs Eg: MTX
Chloramphenicol
ii. Radiation exposure
iii. Infections : • MC : Viral Hepatitis
[Non A/B/C/G Hepatitis]
• Parvo virus B19 inf.
iv. Miscellaneous : • Fanconi's Anemia
(DNA Repair defect
↓
Stem cell development defect)
• Telomere shortening c̄ in stem cell (Abnormal)
• ↓ Telomerase activity c̄ in stem cell

- Pathogenesis :

Extrinsic Abnormality

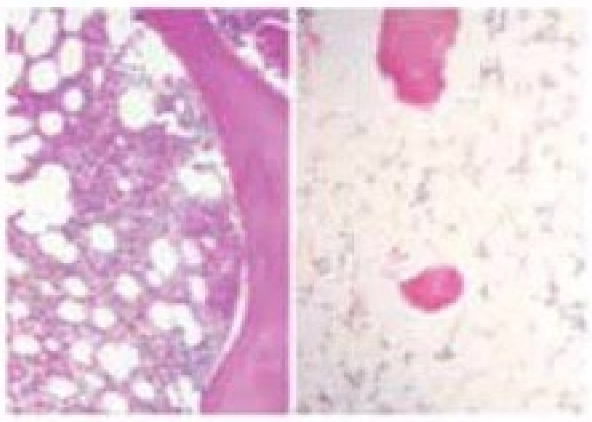
IMMUNE - MEDIATED
- d/t Enviornmental insult on stem cell
↓
Antigenic variations
↓
Activate T_{H1} cells
↓
IFN-γ Cytokine
↓
Damage of stem cell
↓
Aplastic Anemia

Intrinsic Abnormality

IFN-γ (+)
STEM CELL
Upregulation of Apoptotic Gene or Death Receptor
↓
CELL-DEATH
↓
Aplastic Anemia

Peripheral smear : * RBC Count, WBC Count, Plat. Count } ↓ : PANCYTOPENIA
* Normocytic Normochromic Anemia or Macrocytic Normochromic Anemia

BM Biopsy : * FAT Cells 50% : Stem Cells 50% } Normal
* In Aplastic anemia
↑ Fat cells
↓ Stem cells



APLASTIC ANEMIA

A) Normal bone marrow tissue section (hematoxylin and eosin stain).
B) Hypoplastic bone marrow tissue section from a patient with aplastic anemia (hematoxylin and eosin stain).

Classification Aplastic Anemia

Based on pancytopenia

Non-severe
- BM Cellularity <25%.
- Not fulfilling criteria of severe A.A

Severe
- BM Cellularity <25%.
- And any of the following 2 (out of 3)
  - i. Absolute Neutrophil Count : <500/mm^3
  - ii. Platelet count: <20,000/mm^3
  - iii. Reticulocyte count: < 60,000/mm^3

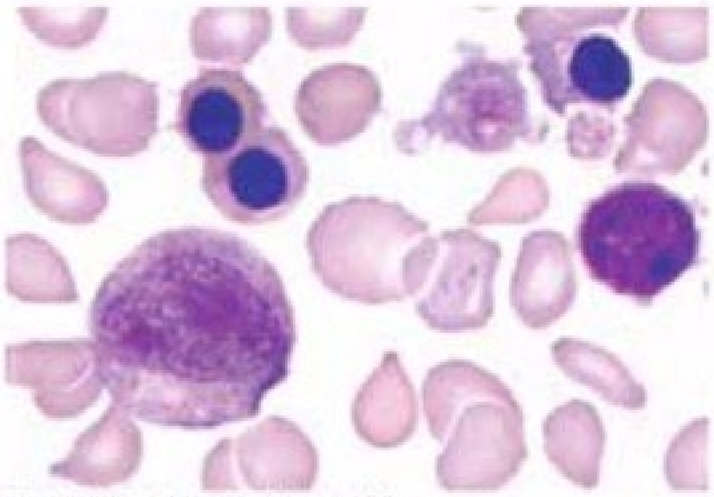
V. Severe
- Same as Severe
- Only Absolute Neutrophilic count : <200 mm^3

Clinical Feature
* Pallor, Fatigue
* ↓ WBC : ↑ infection
* ↓ Plat : Bleeding

Aplastic Anemia Transform into → • MDS • Acute Myeloid Leukemia

Myelopthisic Anemia

- BM Failure
  d/t: Space occupying lesion of BM
- Causes :
  - i. MCC : Metastatic Cancers to BM
    (MC due to BREAST Cancer)
  - ii. Chronic Myeloproliferative disorder
  - iii. Hairy Cell Leukemia
  - iv. Granulomatous inflammation (Eg: TB/Sarcoidosis)
  - v. Leukemia / Lymphoma involving BM
- Peripheral Blood : * ↓RBC, ↓WBC, ↓Platelet } PANCYTOPENIA
  - * Leuko erythroblastic Reaction
    - immature precurssors of WBC, RBC in P.B
      - i. Myelocyte
      - ii. Nucleated RBC
      - iii. Tear drop RBC



MYELOPHTHISIC ANEMIA

Peripheral smear showing a leucoerythroblastic blood picture with a myelocyte (immature WBC), three orthochromic normoblasts (Immature RBC), teardrop erythrocytes, a giant platelet with abnormal morphology, and a micromegakaryocyte.

LEUKEMIA AND LYMPHOMA

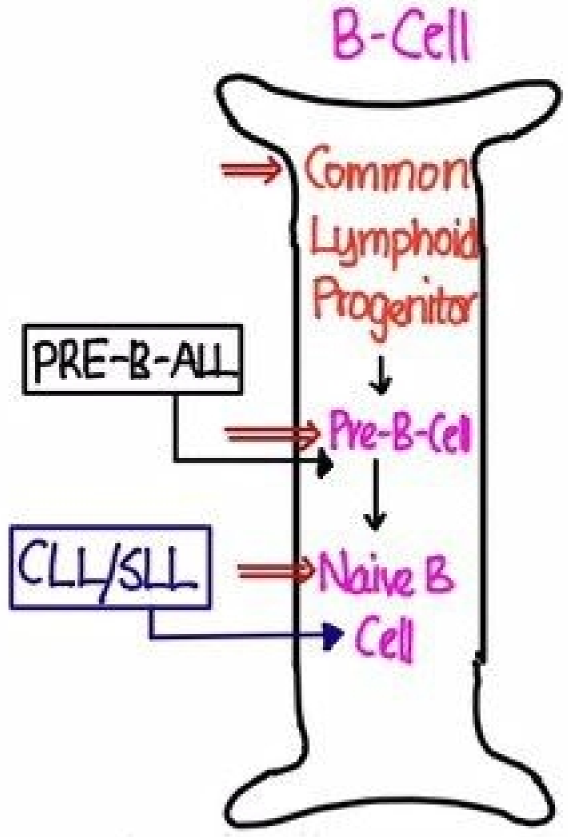
# Tumor of immature WBC
if inolvement of P.B (or) B.M → Leukemia
if inolvement of LN (or) Organs → Lymphoma

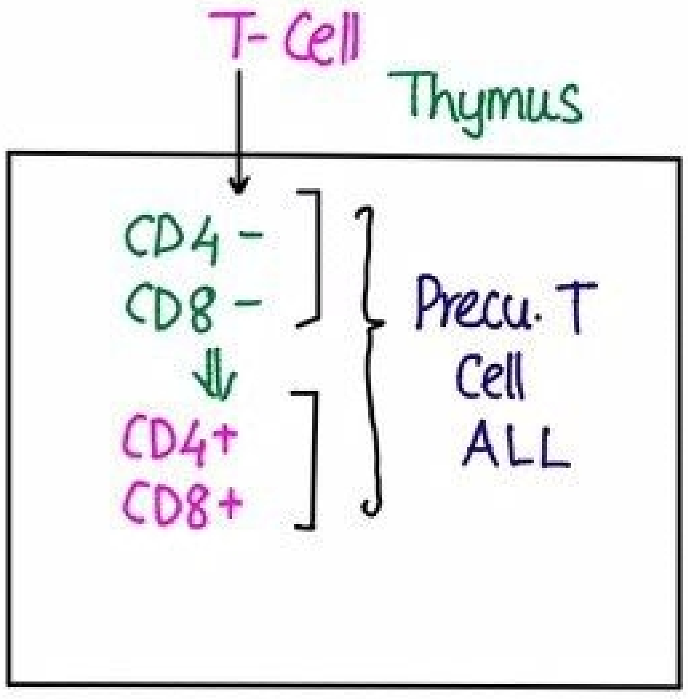
# Leukemia may have lymphoma & vice versa

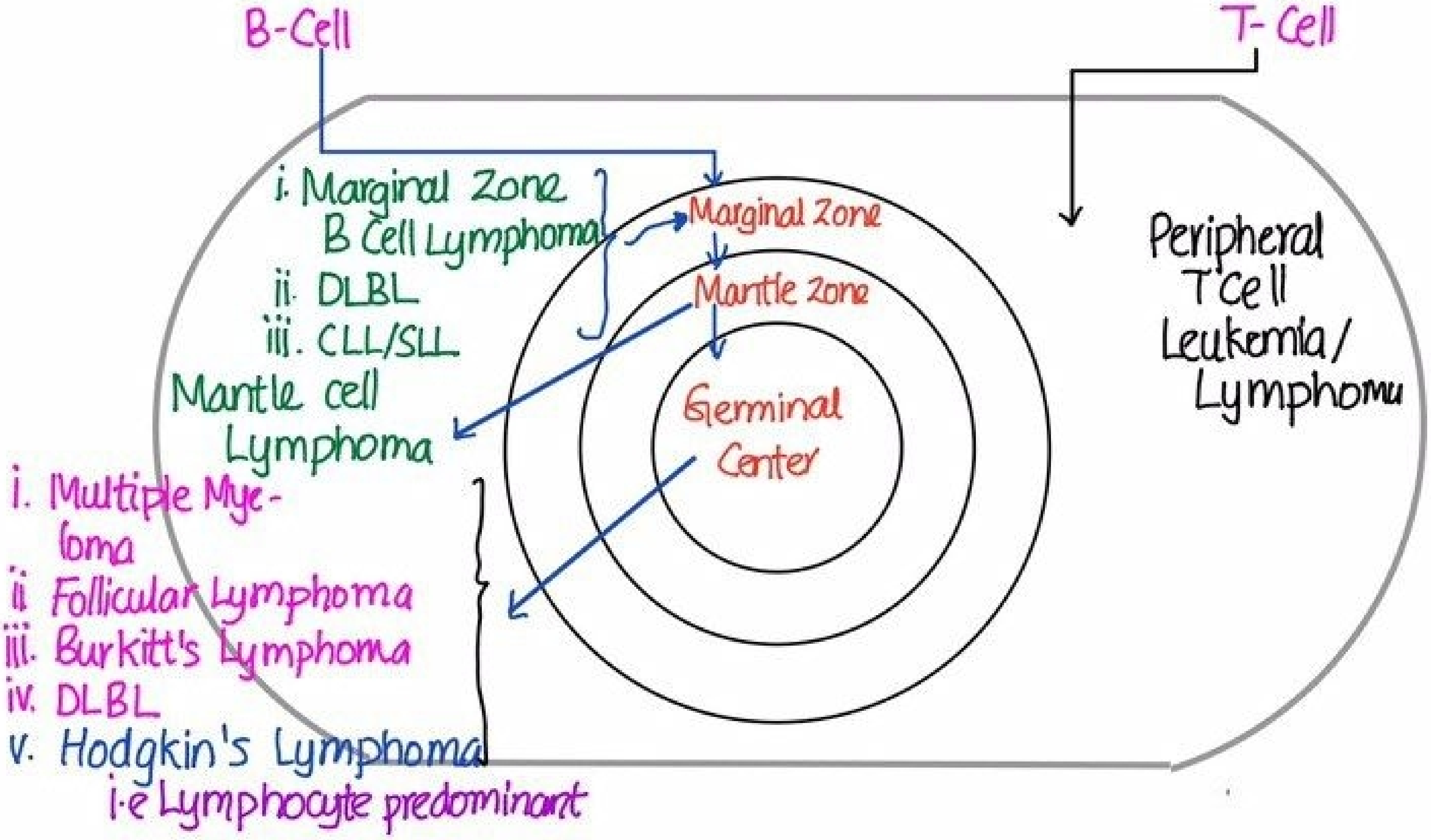
WHO CLASSIFICATION

- HODGKINS LYMPHOMA
- NON-HODGKIN LYMPHOMA
  - B Cell
    - Immature
      Pre B-Cell Leukemia/Lymphoma
      Eg: Pre B ALL
    - Mature
      Peripheral B Cell Neoplasm
      Eg:
      - Mantle cell Lymphoma
      - CLL /SLL
      - Follicular Lymphoma
  - T Cell
    - Immature
      Pre T-Cell Leukemia/Lymphoma
      Eg: Pre T-ALL
    - Mature
      Peripheral T-Cell Neoplasm
      Eg:
      - Mycosis fungoides
      - Anaplastic Large cell Lymphoma

CELLS OF ORIGIN





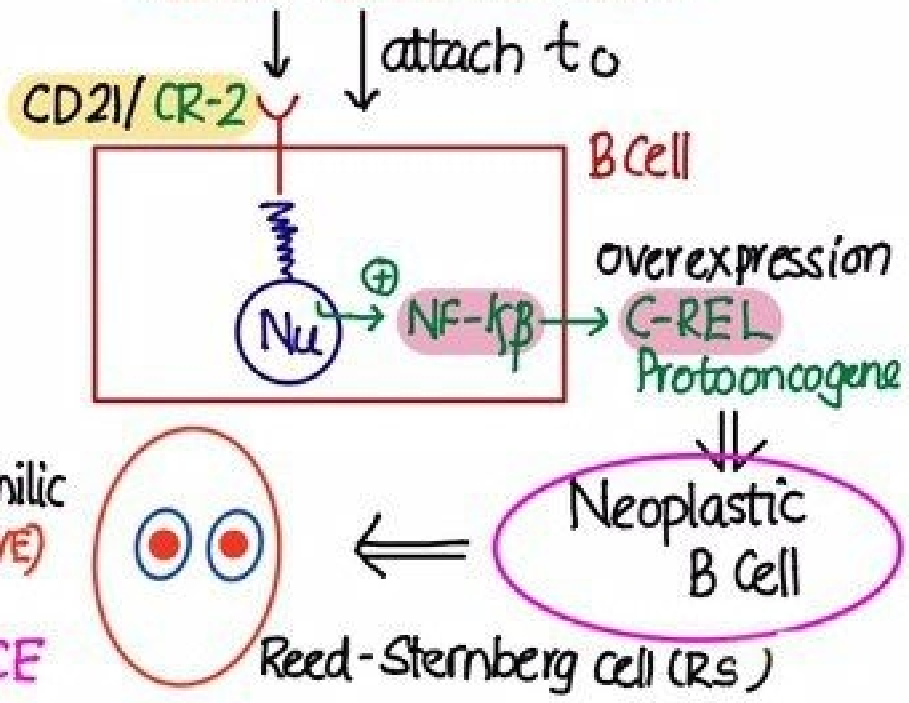


HODGKINS LYMPHOMA	NON-HODGKIN LYMPHOMA
* involve single group of L.N	* involve chain of L.N
* Nodal involvement i.e LN involvement more	* Extranodal
* LN involvement is Orderly spread in contiguity	* No-orderly spread
* Mesenteric LN & Waldeyer Ring is rarely effected	* Mesenteric LN & Waldeyer Ring is commonly effected

Hodgkin's Lymphoma

-Clinical Features :
- Young /Older
- MC Presentation : Painless cervical LN Enlargement
- CYCLICAL FEVER : Pel Ebstein Fever
- PARANEOPLASTIC SYNDROME
  - i. Amylloidosis - Secondary AA Type
  - ii. Alcohol induced LN Pain

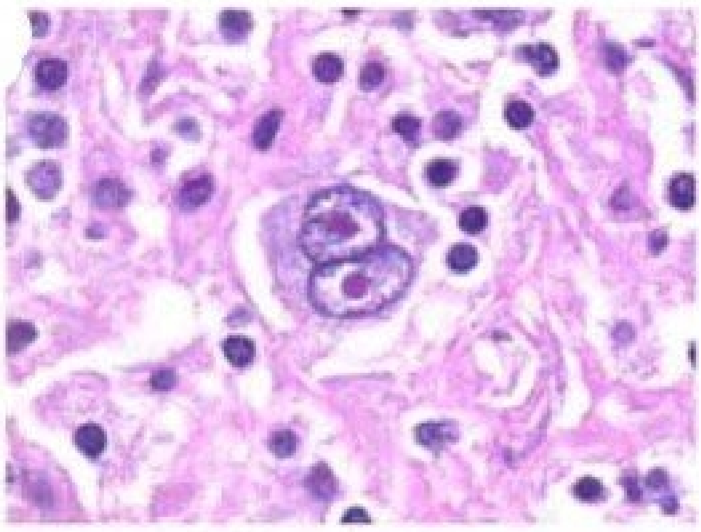
-Pathogenesis : EBV INFECTION → Latent Membrane Protein-1 (LMP-1)



* Large cell
* Mirror like Nuclei
* Prominent Eosinophilic Nucleoli (=OWL-EYE)

⇓

OWL-EYE APPERANCE

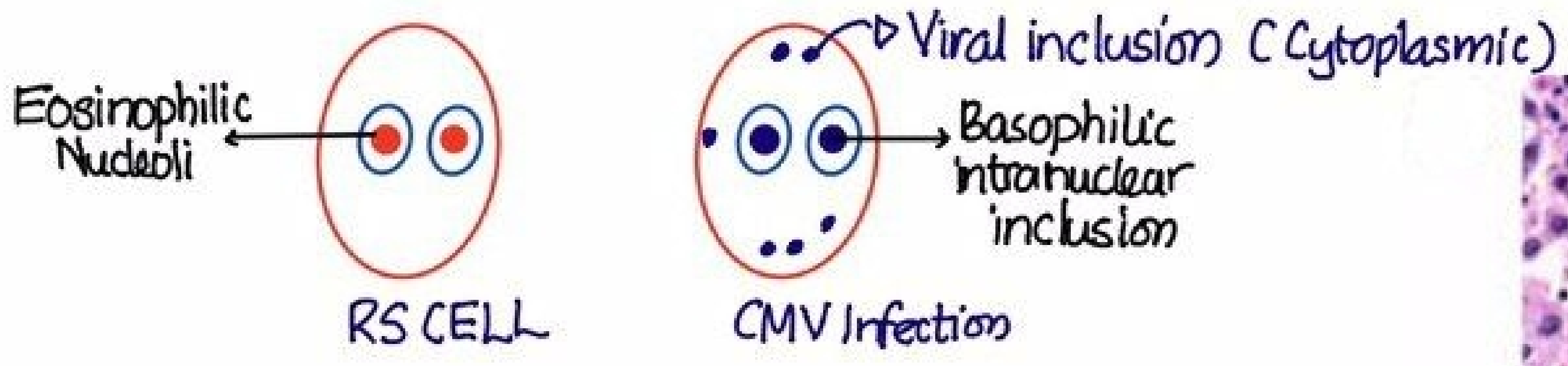


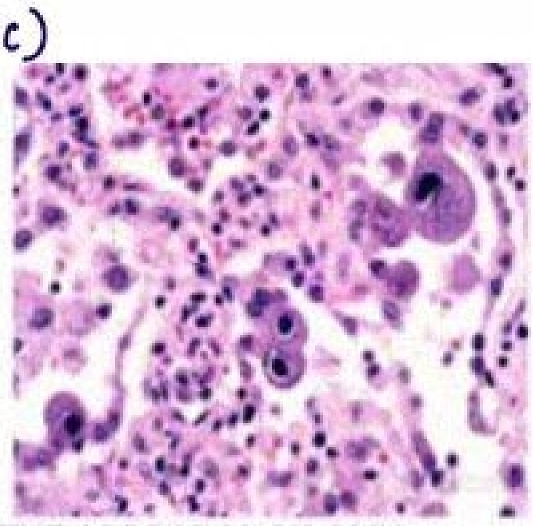
CLASSICAL REED STERNBERG CELLS

Mirror-image nuclei (Owl eye) contain large eosinophilic nucleoli giving owl eye appearence. Seen in Hodgkin's lymphoma. They are CD15+, CD30+.

OWL-EYE APPEARANCE:

- RS Cell
- CMV Infection


Viral inclusion (Cytoplasmic)
Eosinophilic Nucleoli
Basophilic intranuclear inclusion
RS CELL
CMV Infection



OWL EYE APPEARANCE CMV

Mirror-image nuclei (Owl eye) contain large basophilic viral inclusions, giving owl eye appearance.

RS Cell Alone is non-diagnostic

Seen in :
- Infectious mononucleosis
- Non-Hodgkin's Lymphoma
  MC : DLBL (Immunoblastic NHL)
- Hodgkin's Lymphoma

- Histological Diagnosis of HL:

RS Cell + Mixed inflammation in background

RS Cell ↓ Neoplastic

Mixed inflammation ↓ Neutrophil, Lymphocyte, Eosinophil etc. Non-Neoplastic

HODGKIN LYMPHOMA

Based on Immunophenotype of RS Cell

CLASSICAL

i) CD15+ < CD30+

- Nodular Sclerosis
- Mixed Cellularity
- Lymphocyte Rich
- Lymphocyte-Poor
  WORSE-PROG

NON-CLASSICAL

aka NLPHL = Nodular Lymphocytic Predominant HL

i) CD15 − CD30 −

ii) Origin : Germinal Center

↓ marker

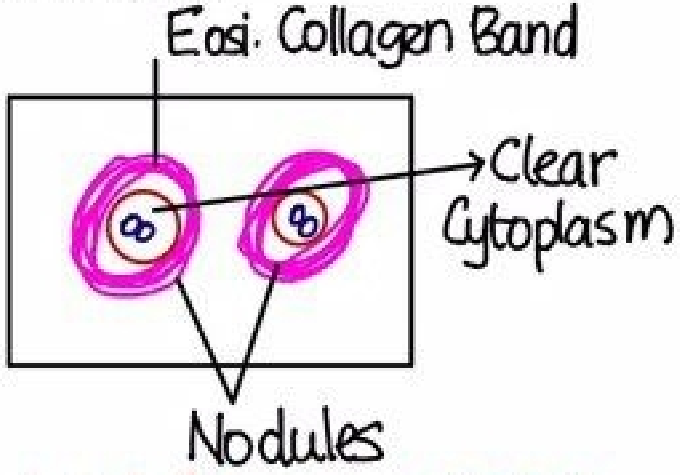
BCL-6

[CD20 + , CD45+]

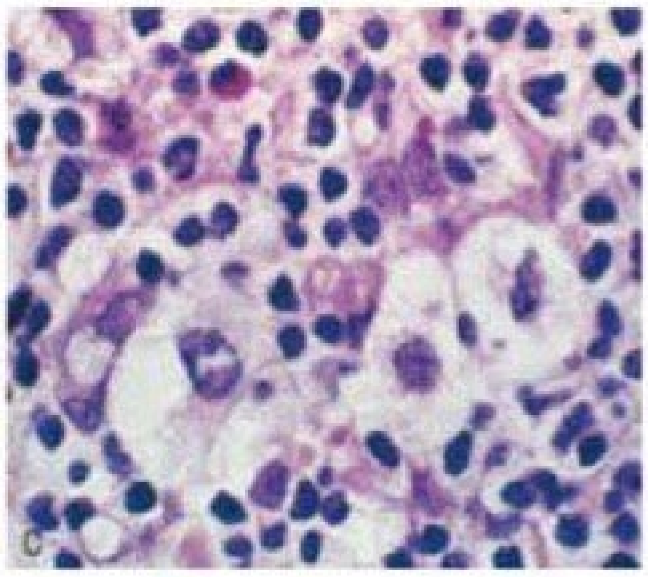
iii) OVERALL BEST PROGNOSIS

Nodular Sclerosis

- * BEST PROGNOSIS
- * Young patient
- * M = E
- * Mediastinal Mass
- * MC type of HL
- * M/E:

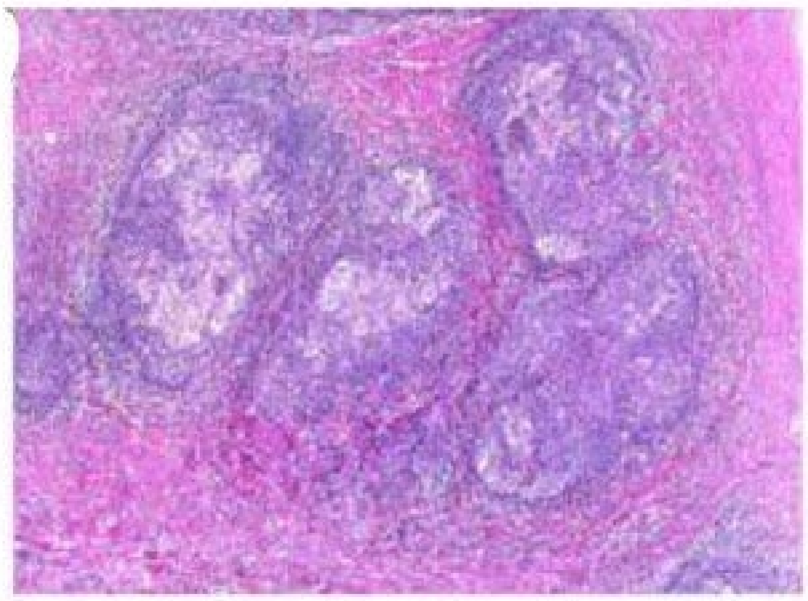


∴ called Lacunar RS Cell



LACUNAR REED STERNBERG CELLS

They have folded or multilobated nucleus and lies within an empty space which is an artifact due to removal of cytoplasm during tissue sectioning.
(Note: clear space around nucleus that's why lacunar)
Seen in Nodular sclerosis HL. (CD 15+ and CD30+).

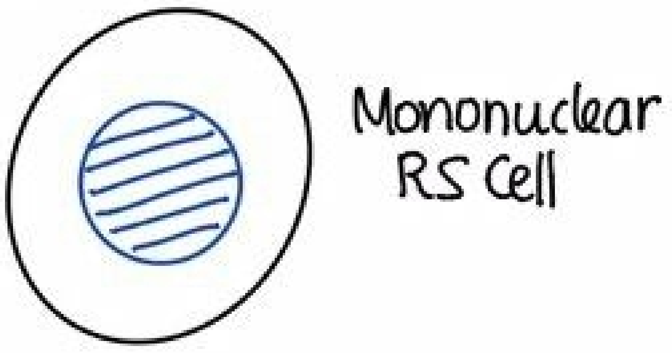


NODULAR SCLEROSIS HL

Low power view showing collagen bands forming nodules within lymph nodes.

Mixed Cellularity

- * MC HL in india or developing countries
- * Biphasic ; Younger & old
- * MC a/w B-Symptoms of HL (=fever, Night sweats)
- * HL mostly a/w HIV & EBV infection
- * M/E:

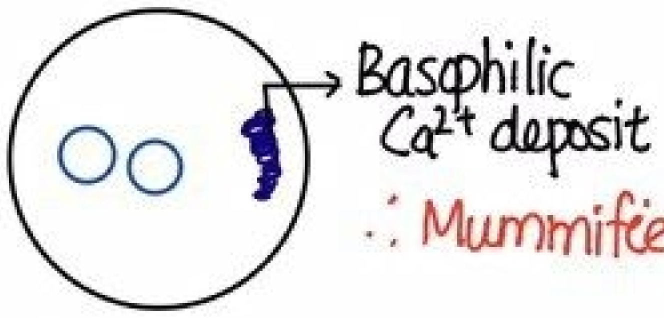


Lymphocyte Rich

- * Good prognosis
- * Mono-nuclar RS Cells

Lymphocyte-Poor

- * WORST Prognosis
- * Young patient
- * M/E: PLEOMORPHIC RS Cells



∴ Mummified R-S Cell

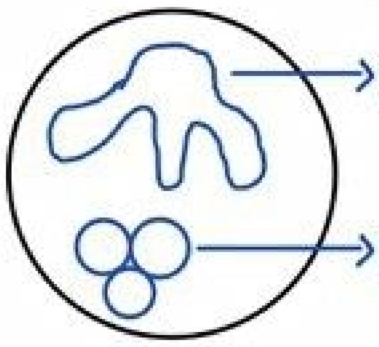
Hodgkin cell : Atypical Histiocytes

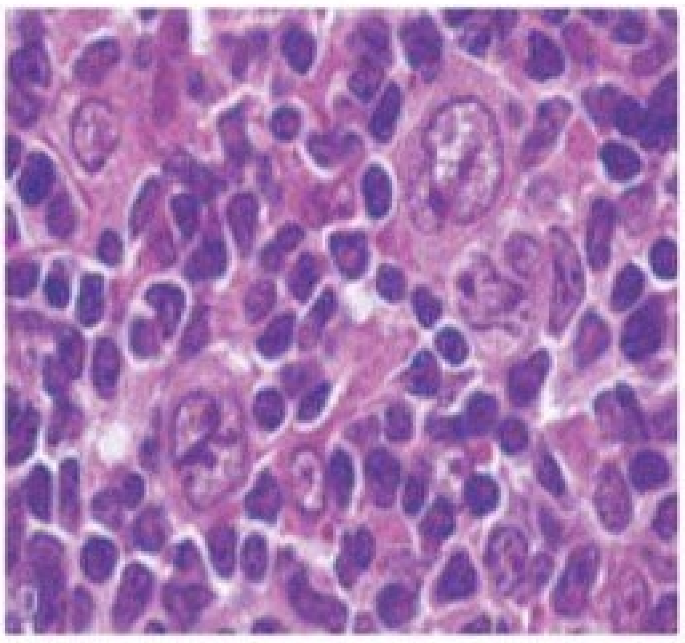
for more notes,join our telegram channel, "latest neet pg notes 2020" or join via link " t.me/latestpgnotes"

Lymphocyte Predominant /NLPHL

- OVERALL BEST PROGNOSIS
- Young patient
- Cervical / axillary LN involvement
- NO A/W EBV INFECTION
- Microscopic Examination

Lymphocyte - Histiocyte rich variant of RS Cells
LH Variant of RS cells
or POPCORN RS Cells





POPCORN REED STERNBERG CELLS
Popcorn Reed-Sternberg cell (lymphohistiocytic variant) with multiple infolded nuclear membranes, small nucleoli, fine chromatin, and abundant pale cytoplasm are present. (Note: Nucleus is like polyp or multilobated like Popcorn). Seen in Lymphocyte-Predominant Hodgkin's lymphoma. CD 20+ but CD15- and CD 30-, BCL- 6+ve (Germinal Centre proliferation marker).

STAGING FOR HL & NHL = Ann-Arbor staging

STAGE - I : Single group of LN involved
or
Single extra Lymphatic organ involved

STAGE - II : ≥2 groups of LN on same side of diaphragm involved
or
Extra lymphatic Organ present

STAGE - III : Group of LN on both sides of diaphragm with or without extra lymphatic organ involvement

STAGE - IV : Diffuse involvement of extra lymphatic organ with or without LN involvement.

Ⓐ Based on clinical features Ⓑ

Absent ← → Present

i. Night sweat
ii. Unexplained wt loss
iii. Unexplained fever

Bad prognostic features

i. Male gender
ii. Age >45 yrs
iii. Hb <10.5 gm%
iv. Lymphocyte ↓↓
Eg: Absolute Lymphocyte count <600/μL
TLC : Lymphocyte <8%
v. Low albumin : <4 gm/dl
Vi. TLC > 15000/mm3
Vii. STAGE-4

NON-HODGKIN'S LYMPHOMA

* Approach toward Acute Leukemia Patient

↓

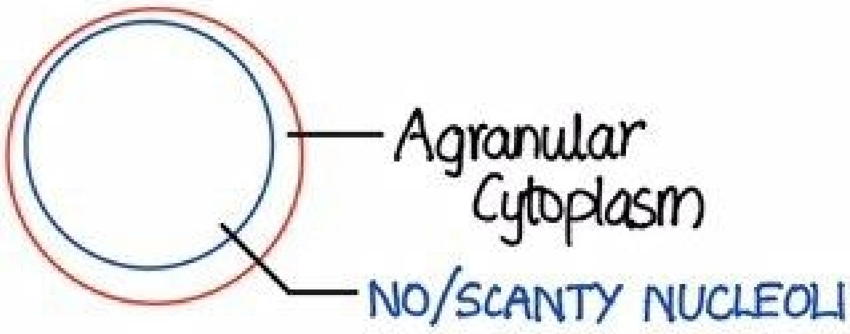
i. Peripheral Smear
ii. BM aspirate / Biopsy
iii. Immunophenotype
iv. Cytogenetics

⇓

↑ BLAST CELL : >20% (WHO) ; >30% (FAB)

LYMPHOBLAST

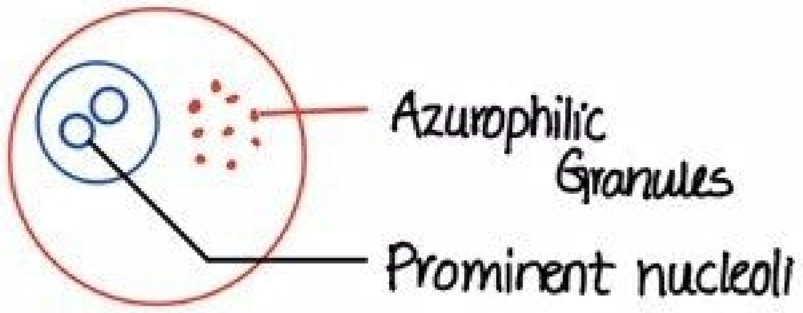
* scanty cytoplasm



Stain : PAS +ve (∵ of glycogen)

MYELOBLAST

* small nucleus



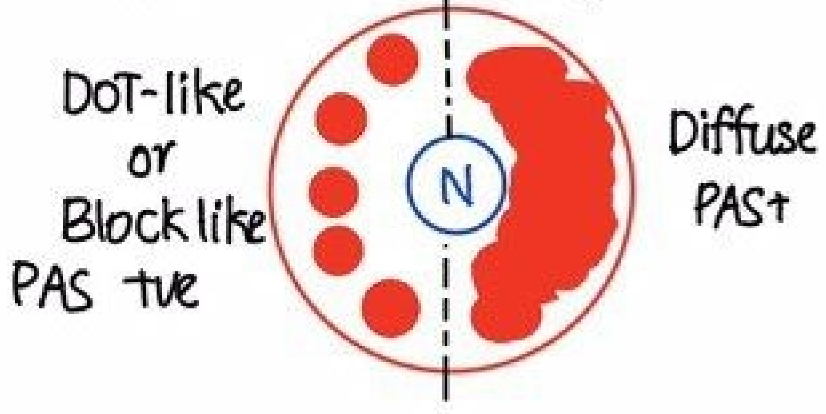
Stain : i. MPO +ve
(MOST. SPECIFIC MARKER/ SENSITIVE MARKER)
ii. Sudan Black-B
Non-specific
iii. Monocytic Lineage
- SBB -ve
- MPO -ve
- Non-specific esterase : +ve (NSE)

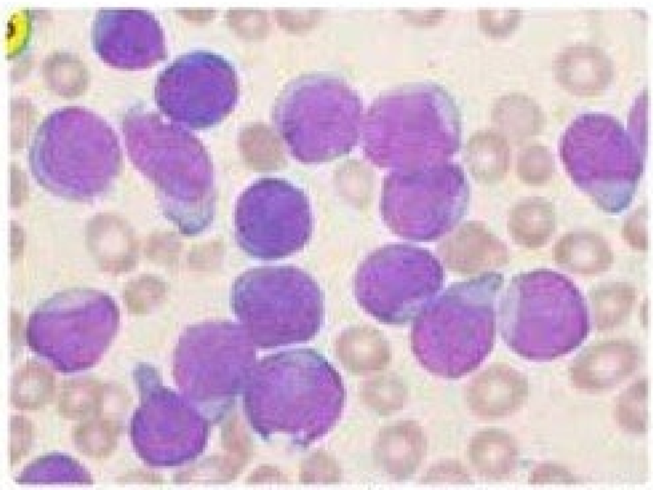
↓

$\boxed{M_3, M_4, M_5}$ → weakly +ve for NSE

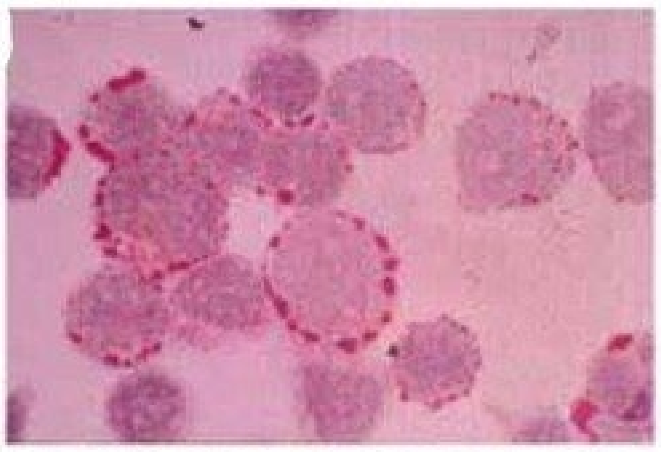
iv. M_6 : Erythroblast
PAS +ve.

Lymphoblast v/s Erythroblast

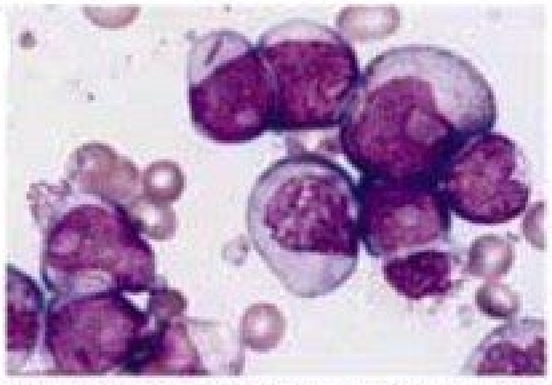




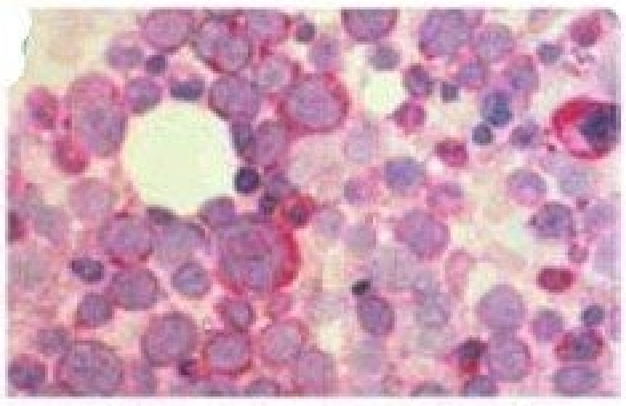
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Lymphoblast will show (2 imp hints)
1) No nucleoli.
2) Agranular cytoplasm.



ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (PAS STAIN)
Lymphoblasts will show "block like" or "dot -like" PAS positivity.



ACUTE MYELOBLASTIC LEUKEMIA (AML)
Myeloblasts will show:
a) Granular cytoplasm and
b) 3-5 prominent nucleoli.



ACUTE MYELOBLASTIC LEUKEMIA (AML-M6 WITH PAS STAINING)
Diffuse PAS positivity seen in Erythroblastic cells.

Auer-Rods :
- Most definitive marker of Myeloid differentiation
- Abnormal azurophilic granules.
- MC seen in M3

Acute Lymphoblastic Leukemia / Lymphoma (ALL)

- Pediatric age group : MC Cancer of Childhood

MC solid cancer of childhood : GLIOMA
MC extracranial solid cancer of childhood : Neuroblastoma

- Tumor of immature B cell
- WHO- 2016

Pre-B-ALL

* MC Type (80-20%)

i. B-ALL a/w HYPERDIPLOIDY
ii. B-ALL a/w HYPODIPLOIDY
iii. B ALL a/w t (9:12)
iv. B-ALL a/w t (12:21)
(ETV-6 to RUNX-1)
v. B-ALL a/w t (1:19)

Provisional Entity
i. B-ALL a/w BCR-ABL-1 like cytogenetics
ii. B-ALL a/w iAMP-21

Pre T-ALL

* 15-20%

Provisional Entity
i. Early Pre-T Cell ALL
ii. NK Cell type ALL

- ETIOLOGY :
  i. Radiation exposure
  ii. Chemical : BENZENE
  iii. Hereditary Syndrome : Down Syndrome
  Turner Syndrome
  Klinfelter Syndrome
  Fanconi's Anemia
  Ataxia Telengectasia

- Pathogenesis :

B-ALL (MC)

* PAX-5 gene mutation

↓

HYPERDIPLOIDY
(MC CYTOGENETIC CHANGE)

* t(12:21) → ETV-6 to RUNX-1
* HYPODIPLOIDY

Clinical Features :
- 2-5 yrs old
- BM / P.B involvement

↓

* Anemia or Pancytopenia

T-ALL

* NOTCH gene mutation

Clinical Features
- 13-17 yrs (Adolescents)
- MC Presentation
  i. Mediastinal mass (= Thymic mass)
  ii. Headache, Vomiting, Seizure
  iii. Testis involvement

Common Clinical Features

i. Anemia : fatig. /irritability
ii. ↓platelet : Bleeding disorder
* CNS
Testicular involvement
Mediastinal involvement
} All are MC a/w ALL than AML
⇓
Poor Prognosis

Diagnosis :

	B-ALL	T-ALL
• Immunophenotype :	i. CD10+ /CALLA ⊕ ↓ Common ALL Antigen Good prognosis ii. C19 – C24 +ve iii. Terminal deoxy Transferase TdT : +ve	i. CD 1,2,5,7 +ve ii. TdT +ve
• Mol. Cytogenetics :	PAX-5 mutation	NOTCH mutation
• Prognosis :	Good prognosis	Bad prognosis

PROGNOSTIC FEATURES OF ALL

GOOD	BAD
i. Age: 2-10yrs	i. <2yr >10yr
ii. White	ii. BLACK
iii. Female	iii. MALE
iv. C/F : Med ⊖/Test ⊖/CNS ⊖	iv. Med ⊕/ Testis ⊕ /CNS ⊕
v. HYPER DIPLOIDY	v. HYPODIPLOIDY
vi. Trisomy 4,7,10 Translocation t(9:12) Translocation t(12:21)	vi. t(8:14) t(9:22)* t(1:19)
vii. B-ALL	vii. T-ALL
viii. CALLA ⊕	viii. CALLA ⊖
ix. Early B-ALL	ix. Pre-B-ALL Mature B-ALL

t(9:22) → form BCR-ABL gene

ALL : Bad prognosis
* mol. wt 190kDA
* stronger tyrosine kinase activity

CML : Good prognosis
* mol. wt 210kDA
* weaker tyrosine kinase activity

Myelodysplastic Syndrome - (MDS)

- Myeloid stem cell maturation defect.

MDS

PRIMARY
- Unknown Etiology
- Onset >50yrs
- Less chance of transformation to AML.

SECONDARY
- 2° to treatment related
- after 2-8 yrs
- aka t-MDS : Treatment related MDS
- POORER PROGNOSIS ↓ ∵ of ↑ risk of AML transformation

- WHO - Classification
  - i. MDS with Single lineage dysplasia
  - ii. MDS with Multilineage dysplasia
  - iii. MDS with Ringed Sideroblast
    - a) with single lineage dysplasia
    - b) with multilineage dysplasia
  - iv. MDS with ↑↑ Blasts (>20%)
  - v. MDS with isolate 5q deletion

  Provisional Entity
  - i. Refractory cytopenia of child hood.

- Etiology :
  - i. Radiation exposure
  - ii. Alkylating Drugs
  - iii. Chromosomal abnormalities / Cytogenetic
    - a) Monosomy 5
      Monosomy 7 : MC in Pediatric age
    - b) Deletion of Chr. 5 (5-) : MC in adults (overall)
      Chr. 7 (7-)
    - c) Trisomy 8

Whenever MDS transform into AML : BAD PROGNOSIS

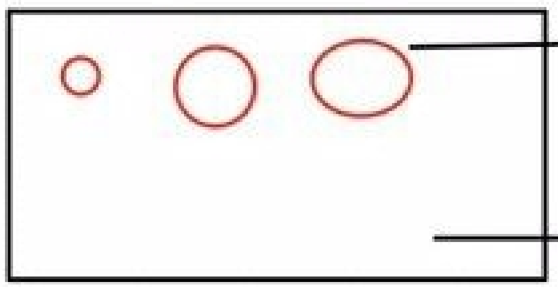
- Pathogenesis :
  - i. Mutation in p53 gene
  - ii. Epigenetics a/w p53
  - iii. ↑ expression of MYC proto-oncogene
  - iv. Loss of 1 copy of Ribosomal protein : RPS-14

⇓

Maturation defect in Myeloid stem cell
↳ • Erythroid
• Megakaryocyte
• Granulocyte

- Microscopic Examination :

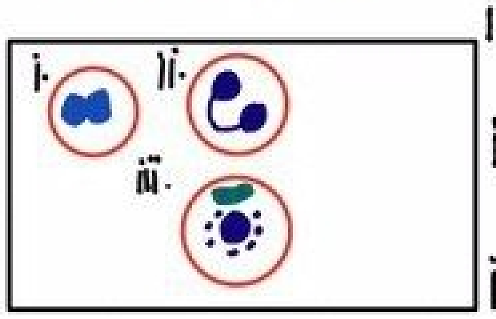
① Erythroid precurssor



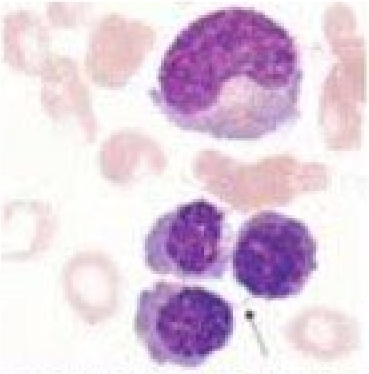
→ Dimorphic RBC
- i. Microcytic
- ii. Macrocytic

→ Macro-ovalocyte

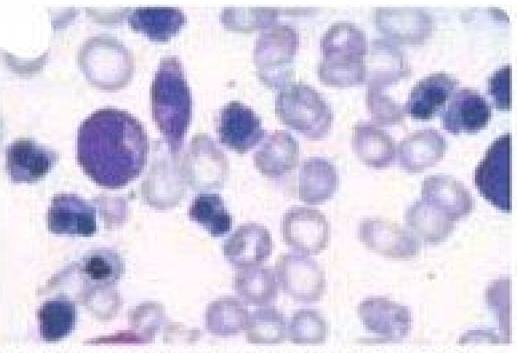
② BM Aspirate



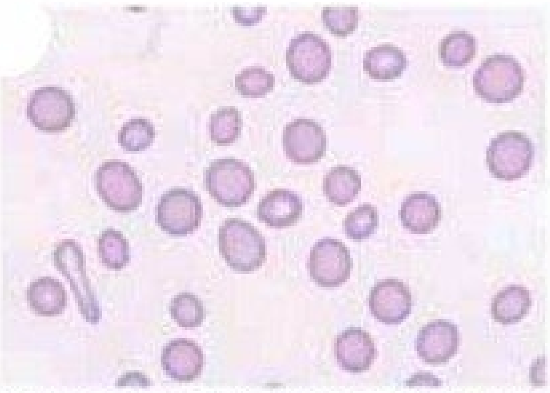
- i. Binucleated RBC
- ii. Nuclear Bridging
- iii. Ringed Sideroblast



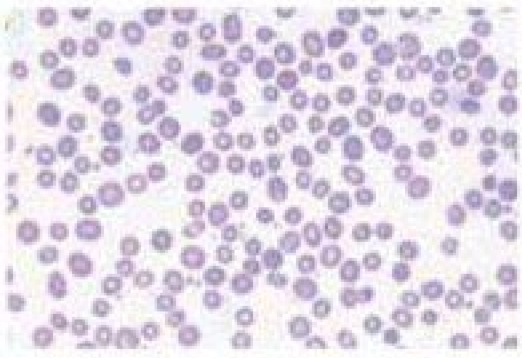
MYELODYSPLASTIC SYNDROME (ERYTHROID SERIES).
Erythrocyte precursor with nuclear bridging.



MDS WITH RBC PRECURSOR NUCLEAR BUDDING
Bone marrow showing erythroid hyperplasia and nuclear budding in erythroid precursors.



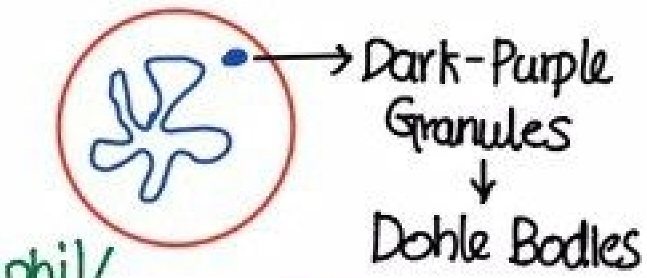
MYELODYSPLASTIC SYNDROME (ERYTHROID SERIES)
Oval macrocytes in peripheral blood

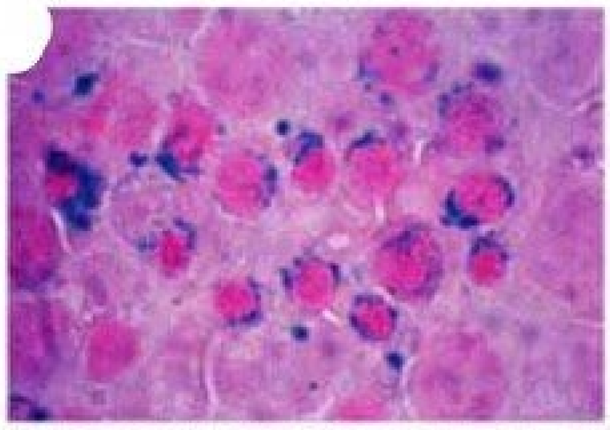


MYELODYSPLASTIC SYNDROME (ERYTHROID SERIES)
Dimorphic RBC population showing both macrocytic and microcytic RBCs.

③ Neutrophil & precurssor

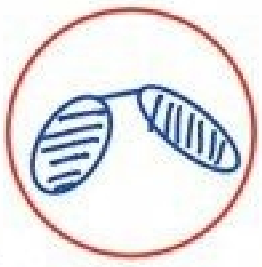
i. Dohle - Bodies
- Made up of dialated RER





MYELODYSPLASTIC SYNDROME (ERYTHROID SERIES)
Ringed erythroblast: Perinuclear Iron accumulation in a ring like pattern due to iron inside mitochondria. Seen in MDS, Sideroblastic anemia and lead poisoning.ring like pattern due to iron inside mitochondria. Seen in MDS, Sideroblastic anemia and lead poisoning.

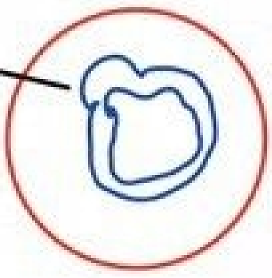
ii. Hypersegmented neutrophil/ Hyposegmented neutrophil

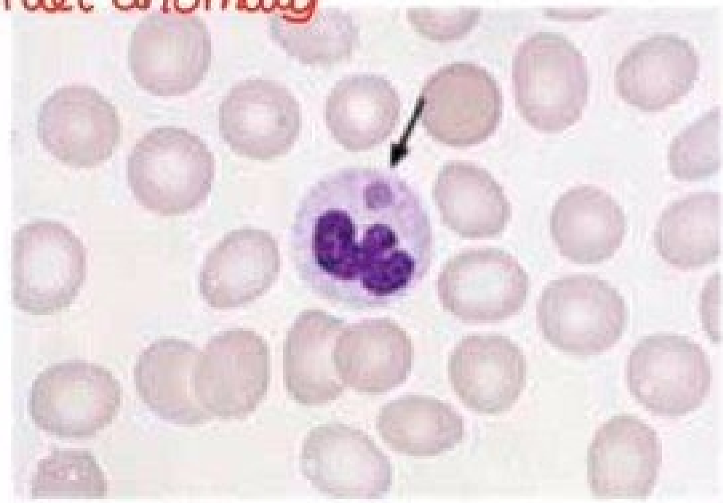


Bilobed Neutrophil
↓
Pseudo-pelger-Huet anomaly

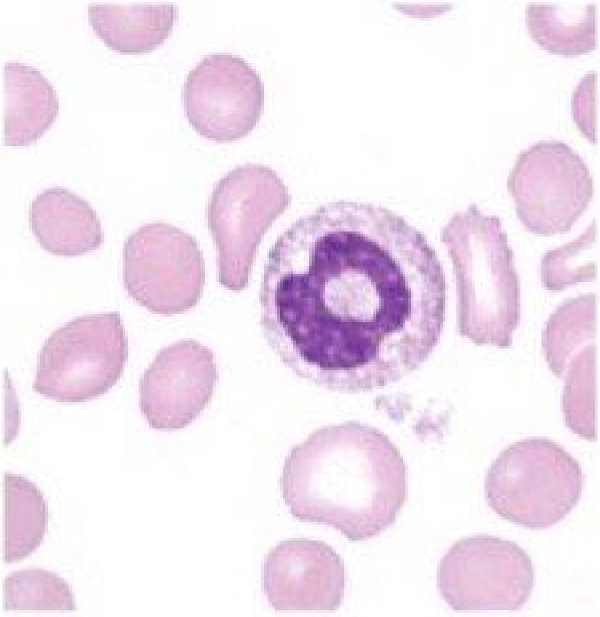
- MDS
- AML ̄c Dysplasia
- accelerated phase of CML

iii. Circular (Donut) Nucleus

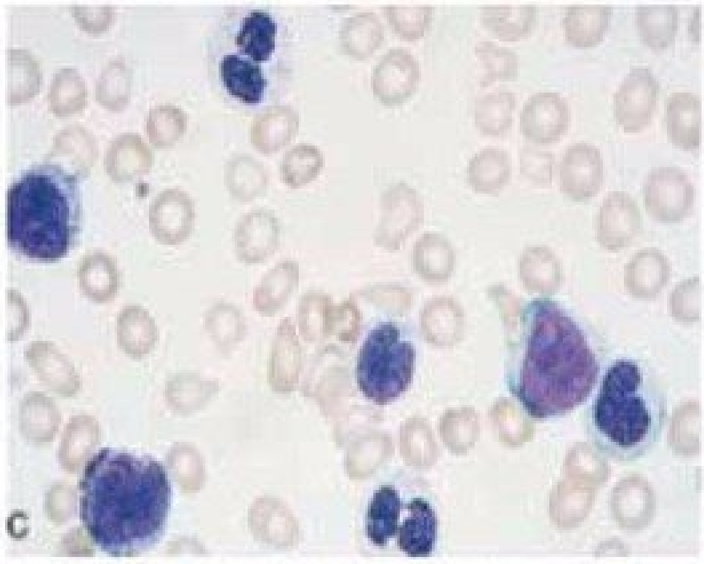




MYELODYSPLASTIC SYNDROME (GRANULOCYTIC SERIES)
Dohle bodies: They are coarse blue granule of cytoplasm made up of dilated rough endoplasmic reticulum. Seen in sepsis; Myelodysplastic syndrome and Chediak higashi syndrome.



MYELODYSPLASTIC SYNDROME (GRANULOCYTIC SERIES)
Abnormal nuclear shapes, neutrophil with circular (donut) nucleus.

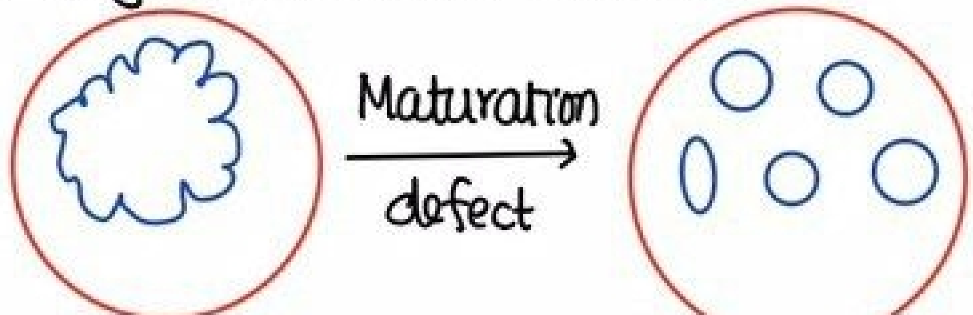


MYELODYSPLASTIC SYNDROME (GRANULOCYTIC SERIES)
Pseudo Pelger Huet anomaly: Neutrophil with bilobed nucleus. It is seen in Myelodysplastic syndrome, Acute myeloid leukemia with dysplastic maturation, and Chronic Myeloid Leukemia (during Accelerated phase).

④ Megakaryocytic lineage

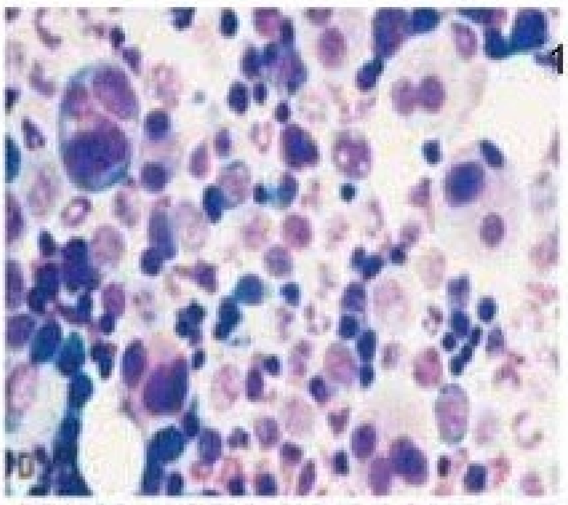
↓

Largest cell on BM Examination



Normal
Fused syncitium like Nucleus

PAWN-BALL Megakaryocyte
Seperated lobules



MYELODYSPLASTIC SYNDROME (MEGA-KARYOCYTIC LINEAGE)

Pawn -Ball Megakaryocyte: Separated lobes of nuclei in megakaryocytes. It is seen in Myelodysplastic syndrome (MDS).

Pseudo Pelger Huet Anomaly : Acquired condition
Pelger Huet Anomaly : Hereditary condition

Acute Myeloid Leukemia

- Pediatric tumor
- Tumor of immature Myeloblast
- Etiology : i. Radiation exposure
  ii. Smoking
  iii. Drugs (= Alkylating)
  iv. Chromosomal Abnormality
    a) Turner Syndrome
    b) Down syndrome
    c) Klinfelter's syndrome
- Pathogenesis :
  1. Central Role : Epigenetics
  2. Genetic mutation
     ↓
     damages Transcriptional Factors required for Myeloid differentiation.
     Eg : t(8:21) ⟶ RUNX-1 Damage
     inv(16) }
     t(16:16) } ⟶ CBF1 β damage
  3. Mutation in Cohesin Gene
     ↓
     ∴ Chromatin disorganisation
     ↓
     Defective myeloid differentiation
- Classification : WHO 2016
  1. AML a/w Genetic Abnormality
  2. MDS Related AML BAD PROGNOSIS
  3. Treatment related AML BAD PROGNOSIS
  4. Not otherwise Specified FAB Class.
  5. Myeloid Sarcoma
  6. AML a/w Down Syndrome

1. AML a/w Genetic Abnormality

a. a/w t(8:21) : • Good prognosis
• Clincalfeatures of M2

b. a/w t(15:17) : • Intermediate - Good prognosis
• Clinical features of M3 /Promyelocytic Leukemia

In M3, Blast $\xrightarrow[\text{release}]{}$ MUCIN (Procoagulant) ⟶ DIC

DIC ↓ b/o
- Prolonged BT
- ↓ PT
- Bleeding
- ↑ aPTT

∴ DIC MC a/w M3

• Auer rods are MC a/w with M3

c. a/w t(16:16) or inv (16) :
- Good prognosis
- Clinical features of M4 with HYPER EOSINOPHILIA (Inf.)

d. a/w Mutant Nucleophosmin Gene (NPM) :
- Good prognosis

e. a/w t(V:11) : V= variable
- Usually treatmented related
- Bad prognosis

Provisional Entities:
i. AML a/w BCR-ABL-1 like Molecular change
ii. AML a/w mutated RUNX-1 Gene

Q. 35 yr old male , BM: Biopsy : 12% blast cell
- Promyelocyte, Myelocyte, Metamyelocyte, Band form et.
- Cytogenetic : t(8:21)

a) ALL
b) AML
c) MDS
d) CML

Diagnosis of AML is confirmed if you find any of the following 3 cytogenetic changes, even if blast count is <20%
i) t(8:21)
ii) t (16:16)
iii) t (15:17)

4. NOT OTHERWISE SPECIFIED (NOS) : FAB Classification

M0 : AML with minimal differentiation
M1 : AML without maturation
M2 : AML with maturation
M3 : Acute Promyelocytic Leukemia
M4 : Acute Myelo-monocytic Leukemia
M5 : Acute Monocytic Leukemia
M6 : Acute Erythroblastic Leukemia
M7 : Acute Megakaryocytic Leukemia

M1–M4 : MPO + Auer rods +

M4 ⇒ MPO + NSE + Auer Rods +

M5 → NSE +

M6 → diffuse PAS + CD71 + → Marker of Glycophorin

M7 → MC AML in Down Syndrome
M7 →
→ CD41;61
→ t(1:22)
⇒ Megakaryocyte → Release Fibrogenic Cytokine (TGF-β) → B.M Fibrosis → RBC WBC Platelet ↓ Pancytopenia

Monocytes → Tissue infiltaration : MC a/w M4 << M5
↓
[GUM HYPERTROPHY
Leukemia Cutis]

5. Myeloid Sarcoma

- Granulocytic Sarcoma or Chloroma
- It's a hematopoeitic stem cell tumor involving soft-tissue
  MC Site : Orbital / Periorbital tissue
- Poor prognosis

in a suspected case of chloroma : PERIPHERAL SMEAR (1st investig)
⇓
Because of Myeloblast ⊕
(Chloroma MC a/w AML
can also a/w · MDS
· CML)

Then do immunophenotype ←
- CD117 : BEST CD Marker Myeloid
- MPO : MOST SPECIFIC
  ↳ BEST
- CD34 +, CD43 +

↓

Cytogenetics : t(8:21)
Chloroma MC a/w M2

Clinical Features :
- Anemia : Fatigue, irritability
- ↓ Platelet → Bleeding (Most striking)
- ↑ infection
- Gum Hypertrophy
- Leukemia cutis.

Chronic Lymphocytic Leukemia (CLL / SLL - Small lymphocytic Lymphoma)

diagnosis is not by Bone Marrow Biopsy/Aspirate in Chronic Leukemia
↓
Only for Prognosis

- Clinical features : · Males
  - 60yrs ⊕
  - MC presentation : LN Enlargement ↑
    Spleenomegaly ↑ } CLL >> CML
    ↓
    Usually LN ↑ ⊖
- Diagnosis : Peripheral Smear
  - ↑ atypical lymphocytes
  - Absolute Lymphocyte count > 5000/mm³

⇓

next Flowcytometry : IOC for CLL Because
i) BEST FOR DETECTION OF LYMPHOCYTOSIS
ii) Immunophenotype can also be conducted

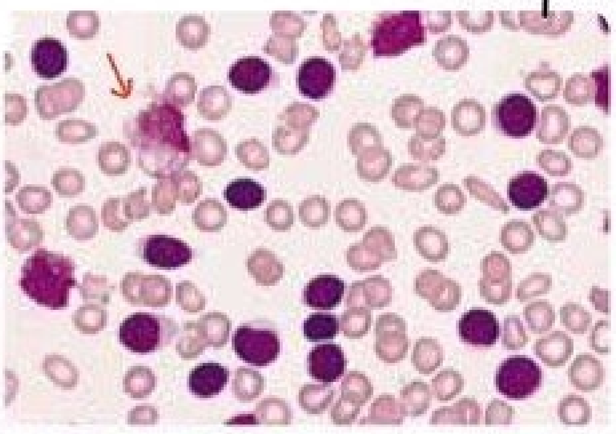
CLL → B-CELL (80%)
CLL → T-CELL (20%)

∴ # CML : CD 5 + (T cell)
CD 23 + (B Cell)

differential diagnosis : Mantle cell Lymphoma (60M, LN↑)

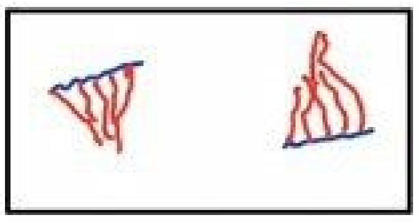
but CD 5+
CD 23−

- On peripheral smear



CLL (SMUDGE CELLS)

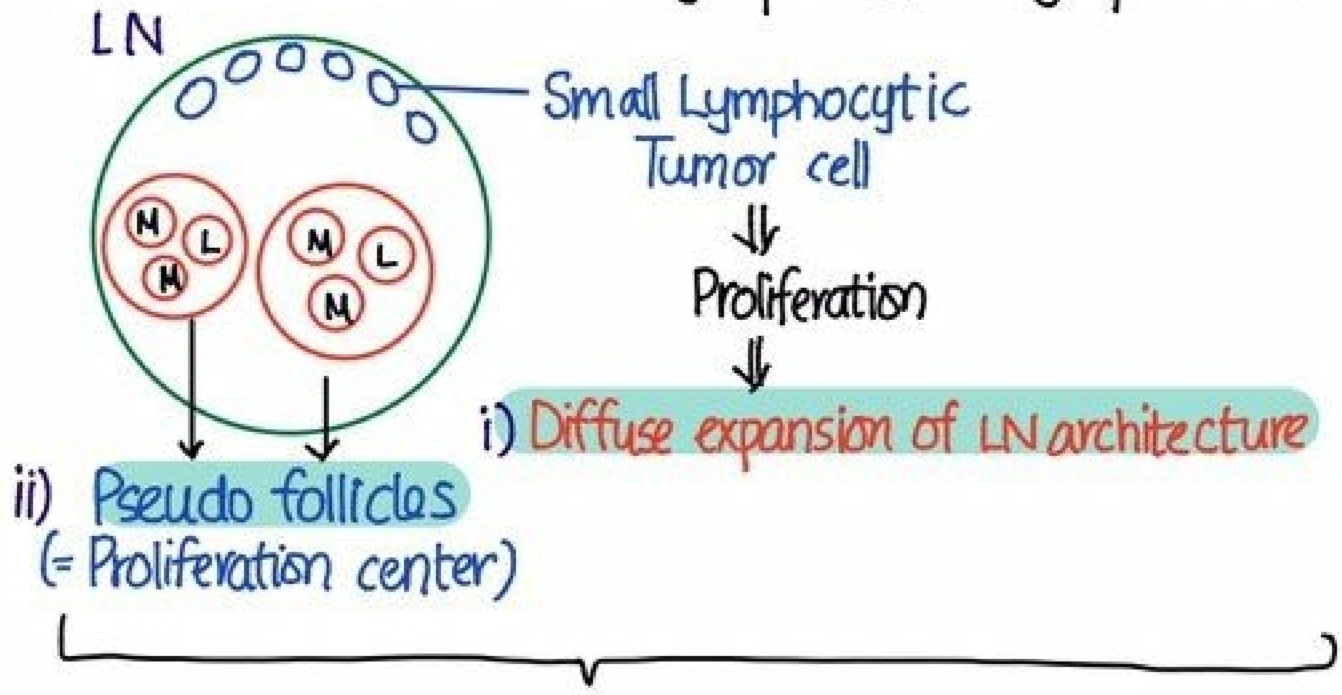
Smudge cells are also known as Parachute cells or basket cells. Smudge cells (abnormal lymphocytes) are slide artefact formed by deficiency of cytoskeletal protein Vimentin, which is required for rigidity and integrity of cells.



i) SMUDGE CELL:
- Charachteristic but not diagnostic
  Also seen in
  - CLL
  - Acute Leukemia
  - Septicemia
- aka BASKET CELL
  PARACHUTE CELL

ii) Warm type of AIHA

⇒ if LN is involved Small Lymphocytic Lymphoma (SLL)



Small Lymphocytic Tumor cell
⇓
Proliferation
⇓
i) Diffuse expansion of LN architecture

ii) Pseudo follicles
(= Proliferation center)

Diagnosis of SLL

# Poor- Prognostic factors of CLL	Good Prognostic Factors
i. No somatic Hypermutation	i. Somatic Hypermutation
ii. Expression of ZAP-70	ii. Absent
iii. Cytogenetic changes : Rare a) Trisomy 12 b) Loss of chr 11, 17 c) NOTCH - 1 gene mutation	iii. Cytogenetic changes a) Deletion 13q : MC Cytogenetic change b) NOTCH-1 gene mutation absent
iv. Transformation a) PRO-LYMPHOCYTIC LEUKEMIA * worsening of cytopenia * massive spleenomegaly * Peripheral Blood : Rich in Prolymphocytes b) RICHTER'S TRANSFORMATION * SLL ⟶ DLBL (MC NHL) ↱ Poor prognosis * Rapidly ↑ mass in LN/spleen	

Chronic Myelo Proliferative Disorder - CMPD

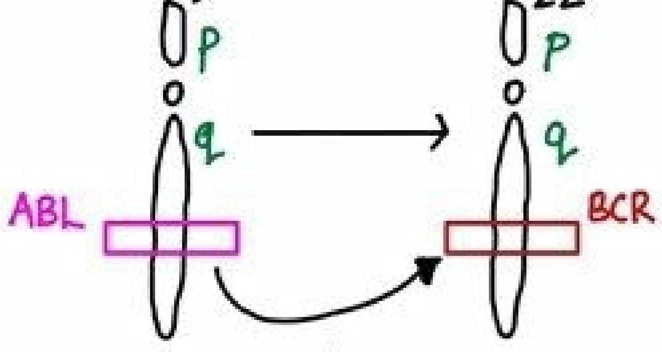
- ↑ Proliferation of Erythroid, Megakaryocytes, Neutrophil.
- This is a group of disorders include
  - i. Chronic Myeloid Leukemia
  - ii. Polycythemia Vero
  - iii. Essential thrombocytosis
  - iv. Primary myelofibrosis
  - v. Systemic mastocytosis
  - vi. Chronic Neutrophilic Leukemia
  - vii. Chronic Eosinophilic Leukemia
- These are having Common pathogenesis :

Abnormal activation of mutated Tyrosine-Kinase
↓
Abnormal Myeloid stem cell proliferation

- Common Clinical Proliferation: i. Abnormal marrow cell proliferation
  - ii. Spleenomegaly, Hepatomegaly [Extramedullary Hematopoeisis]
  - iii. SPENT PHASE
    - initially all precurssors cell ↑
    - ↓
    - Release Fibrogenic cytokine
    - ↓
    - BM Fibrosis → P/S : Pancytopenia
  - iv Transformation in to acute leukemia

1. Chronic Myeloid Leukemia - CML

- MC type of CMPD
- Clinical Features :
  - 60yr or more ; M>F
  - Peak age group : 50-70 yrs
  - Seen in Pediatric, Juvenile or adults
  - Massive Spleenomegaly without peripheral LN enlargement
  - In a known case of CML, sudden, painful, LN↑
    - ↓
    - Suggestive of Blast crisis : BAD PROGNOSIS
- Pathogenesis : Translocation Chr 9 ⟶ Chr. 22
  - ABL ⟶ BCR



↓

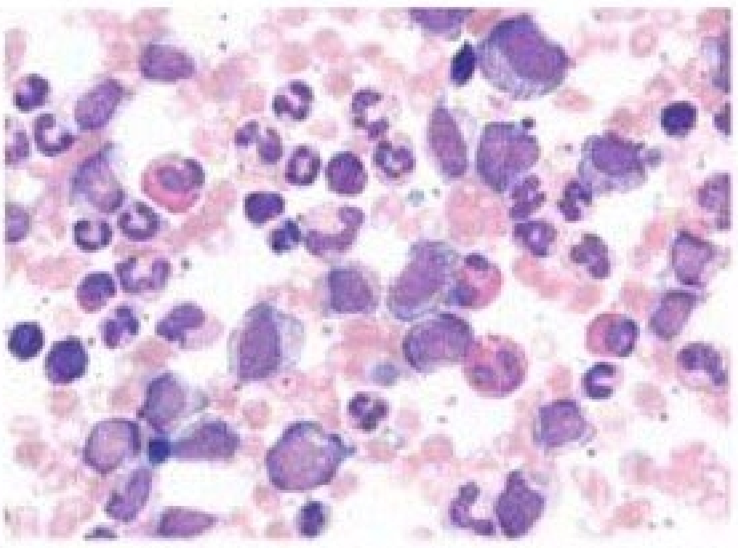
Abnormal Tyrosine Kinase activity ← { BCR-ABL Fusion gene [Chr 22q] Philadelphia Chromosome

- Peripheral smear : ↑ in count of $\underbrace{\text{Neutrophil}}$, Eosinophil, Basophilia, platelet

↓

Immature Cell ≫ Mature Cell } Shift to the Left

- Promyelocyte
- Myelocyte
- Metamyelocyte
- Band form



CHRONIC MYELOGENOUS LEUKEMIA

The peripheral blood shows neutrophilia with prominent left shift (Immature neutrophils), eosinophilia, and basophilia. Typically, numerous myelocytes and segmented neutrophils predominate.

Investigation of Choice : CYTOGENETIC STUDY (FISH >> PCR)

- Ph' / BCR-ABL / t(9:22)

* Phases of CML / Triphasic Leukemia

i. Chronic Phase	ii. Accelerated phase	iii. Blast crisis
• MC presentation • Blast Cell <10% ↓ but BM is not dx ∴ CYTOGENETICS Philadelphia Chr.	* IF one or more of the following present • Blast count = 10-19% • Basophil = > 20% • Thrombocytosis / Thrombocytopenia not-responding to treatment • Massive Spleenomegaly not-responding to treatment • Duplication of Ph' ⊕ Trisomy - 8	• Blast Cell : >20% • Presence of Extramedullary Blast cells present. i.e organ/soft-tissue involvement • Known case of CML ō CHLOROMA ↓ BLAST CRISIS • Large clusters of blast cell on BM Biopsy

Chronic Myeloid Leukemia	Leukemoid Reaction
* TLC ↑ : > lac/mm³	* Increase in TLC > 50,000/mm³ < 1 lacs/mm³
	* a/w : Septicemia Severe infection Burns Down syndrome OCP taking female
* Clinical Examination : a) Organomegaly b) P. B : ↑ Neutrophil, Eosinophil, Basophil, Platelet ↑ N° (immature > mature) c) Cytogenetics : Ph' ⊕	* Clinical Examination : a) Organomegaly absent b) P.B ↑ Neutrophil. Ⓝ Basophil, Eosinophil, Plat. ↑ N° (Mature cell > Immature cells) c) Cytogenetic : Ph' ⊖
* LAP = NAP Score : Decreased except : BLAST CRISIS ACCELERATED PHASE	* LAP = NAP score : Increased

LAP = Leuckocyte Alkaline Phosphatase

2. Polycythemia Vera

# mutant tyrasine kinase JAK-2

↓

↑ granulocyte, RBC, Platelet count in BM & P.B

BM ↓ PANMYELOSIS

P.B ↓ PANCYTOPENIA

- Diagnosis : All 3 major criteria
  or
  First 2major criteria + Minor criteria

MAJOR CRITERIA	MINOR CRITERIA
i. Hb level M : >16.5 g/dl F : >16 g/dl	EPO $\xrightarrow{\oplus}$ CFU-E ↓ ↑RBC mass Ⓝ
ii. Panmyelosis on BM biopsy ↑ Megakaryocyte Granulocyte prec. Erythroid	i. ↓ EPO ∵ due to ↑ RBC mass
iii. Presence of JAK-2 mutation at EXON-12	

- Clinical features : i. ↑ RBC, ↑ Platelet, ↑ Granulocyte } ↑ congestion of BV
  ↓
  ↑ viscocity
  ↓
  ① Visual deformality

  ii. ↑ Basophil → ↑ Histamine
  ↑ Mast cells
  Histamine ↓ ② Peptic ulcer : Recurrent episodes
  ↓ ③ Intense pruritus & intense itching
  d/t exposure to extreme temperature

  ④. 2%. PV transform into AML
  ⑤ Spent phase → Pancytopenia
  Massive Hepatospleenomegaly

3. Essential Thrombocytosis

- Mutant Tyrosine Kinase : JAK-2 /CALR /MPL $\xrightarrow{\oplus}$ ↑↑ Megakaryocytes
- Diagnosis :

MAJOR CRITERIA

- * Platelet count >4.5 lacs/mm3
- * ↑ Megakaryocyte in BM
- * Not meeting WHO Criteria of ML, PV, PMF or any other Myeloid Neoplasm
- * Mutations in JAK-2, CALR MPL

MINOR CRITERIA

- * no evidence of Reactive thrombocytosis

Dx : All 4 Major criteria
or
First 3 major + Minor

- Clinical Features : ↑ Platelet in arterioles
↓
Thrombosis
↓
Occlussion
↓
i. Throbbing & Burning sensation in both hands & feets
called as Erythromelalgia
Found in ET & PV
↓ Charachteristic
ii. Milder or No SPLEENOMEGALY
iii. Transform in to Acute Leukemias

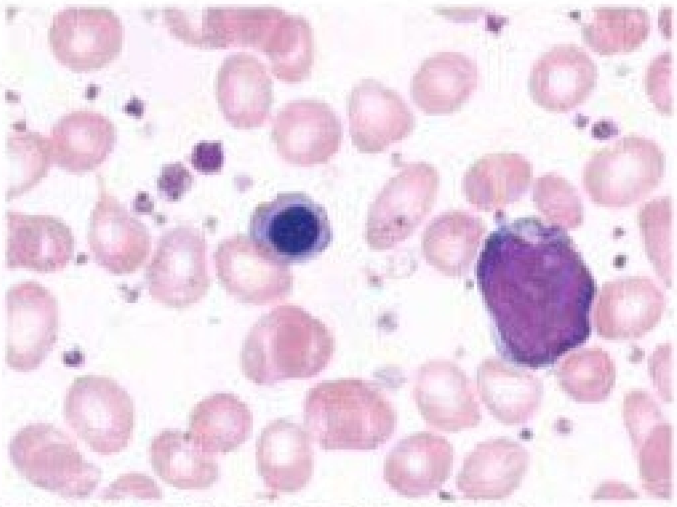
4. Primary Myelofibrosis

- BM Fibrosis + Atypical Megakaryocytes in BM
- Diagnosis:

MAJOR CRITERIA	MINOR CRITERIA
i. ↑ atypical megakaryocytes in BM + ↑ Reticulin fibers causing BM Fibrosis	i. Hb ↓
ii. NOT meeting WHO criteria of CML/PV/ET/or any other myeloid neoplasm	ii. TLC > 11,000/mm^3
iii. Presence of mutations in JAK2, MPL, CALR	iii. Leuko-erythroblastic picture in Peripheral smear
	iv. ↑ LDH

Dx : All 3 major criteria
+
any of the minor

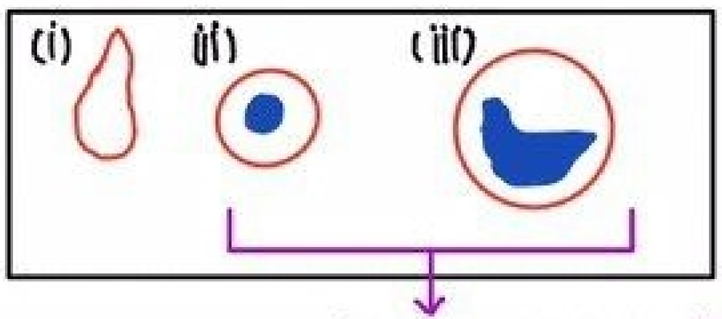
- Clinical Features : i. Extramedullary hematopoeisis
↓
Massive spleenomegaly
ii. Peripheral smear : PANCYTOPENIA



PRIMARY MYELOFIBROSIS (PS)
Peripheral blood shows characteristic findings of Leuko-erythroblastosis with rare blasts, nucleated red blood cells, large platelets, and teardrop-shaped red cells (dacrocytes).

(i) Teardrop RBC = Dacryocytes

(ii) Immature RBC



(iii) Immature WBC

Leuko-erythroblastic picture.

Mantle cell Lymphoma

- Origin : Matle zone of L.N
- These are B-Cell type of Lymphoma
- M > F ; > 60 yrs
- MC Presentation : Painless cervical LN Enlargement

- Charachteristic presentation : Lymphamatoid Polyposis
  ↓
  - It's a pattern of spread
  - Tu cell infiltarating into mucosa of intestine

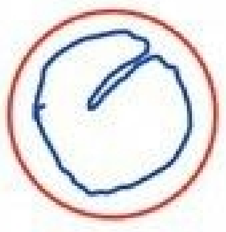
  ⇓
  POLYP-LIKE LESION
- Diagnosis : i. Immunophenotype
  - [CD5+ → Marker of Mantle zone
  - CD23 −]

  ii. Cytogenetics : t(11:14) is diagnostic
  ↳ Cyclin D1/BCL-1 overexpression)

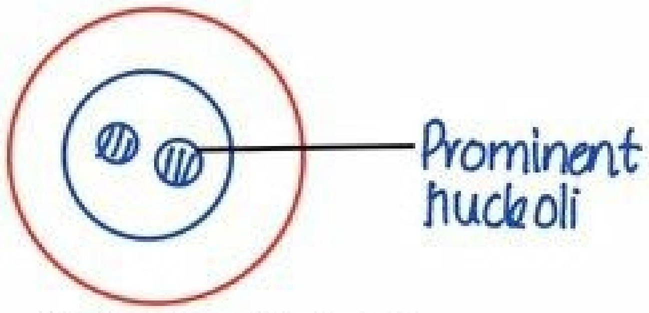
  CYCLIN D-1 Negative MCL
  ↓
  SOX-11 confirm diagnosis

Follicular Lymphoma

- B cell type of Lymphoma ; Cell of origin : Germinal center of LN
- Middle aged : 30-45 yrs ; M>F
- MC Presentation : Painless generalised LNAP
- Lymph node Biopsy



CENTROCYTES
* cleaved nuclei
* aka Buttock cell
* can be seen in P.B



CENTROBLAST
* large cell

- Immunophenotype
  - CD10+ BCL-6 : Marker of Germinal center
  - CD19+
- Cytogenetics : t(14:18)
  ↳ Overexpression of Cyclin D_2 /BCL-2

Burkitt's Lymphoma

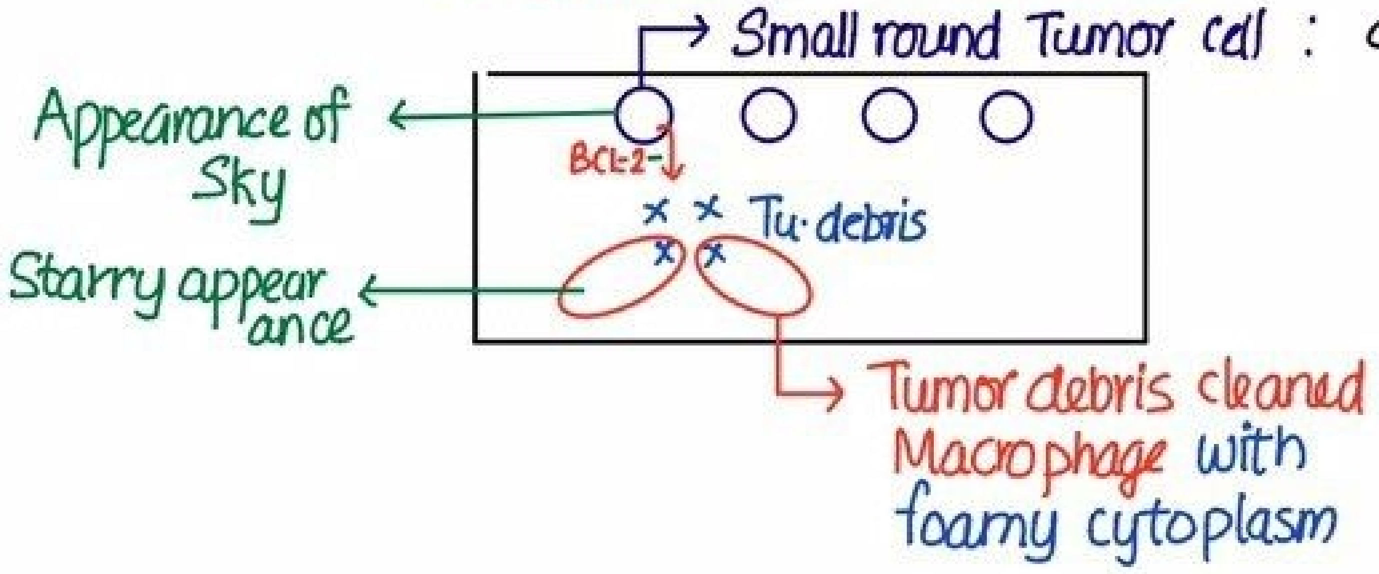
- Mature B-Cell Lymphoma ; Origin : Germinal Center
  - Mature ↓ CD34⊖
  - B-Cell ↓ Ig⊕
- CHEMOSENSITIVE ; BUT AGGRESSIVE & POOR PROGNOSIS
  ∵ i) ↑ affinity for CNS involvement
  ii) Maximum proliferative index
  ↓
  ∴ MC Cause of Tumor-Lysis syndrome

- Clinical Features :

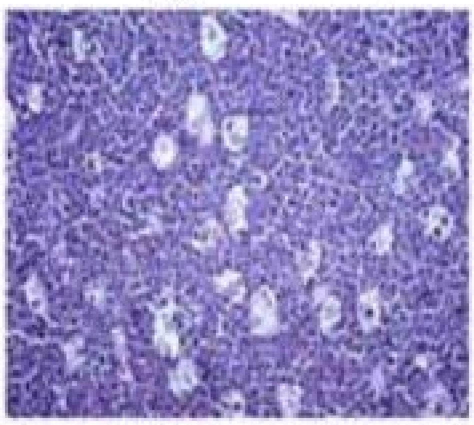
Endemic Type	Sporadic Type	HIV a/w Burkitt Lymphoma
• Pediatric age group : MC • African • MC a/w EBV inf. • MC Site : Face (Madible)	• MC in adults • Less commonly a/w EBV infection • MC Site : Abdomen (Ileocecal mass)	

BL is BCL-2 -ve & BCL-6 +ve
↓
∴ ↑ Rate of apoptosis

- LN Biopsy : STARRY-SKY APPEARANCE

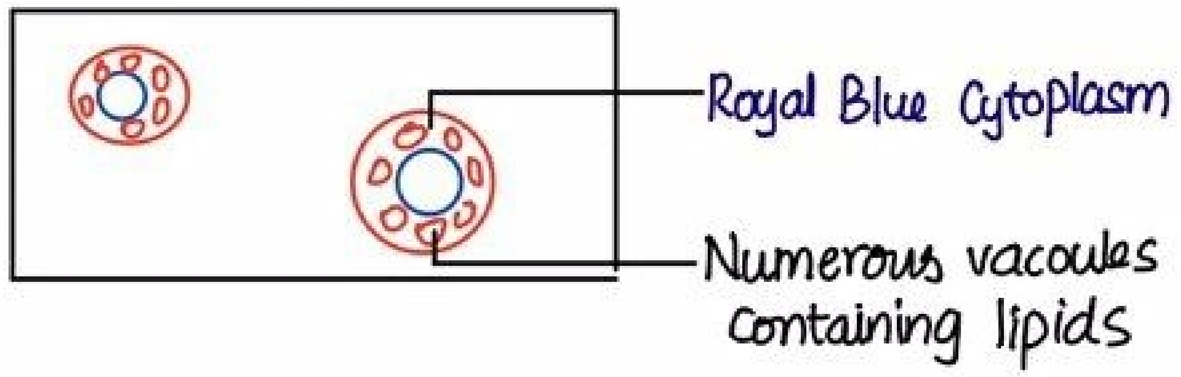


d/d :
- CLL/SLL
- BL
- Neuroblastoma
- Small cell ca Lung
- Wilm's Tumor
- Ewing's Sarcoma



BURKITT'S LYMPHOMA
Showing "starry sky appearance" due to tingible body macrophages ("stars") against background of small round blue tumor cells (sky). Translocations seen are t(2;8); t(8;14); t(8;22).

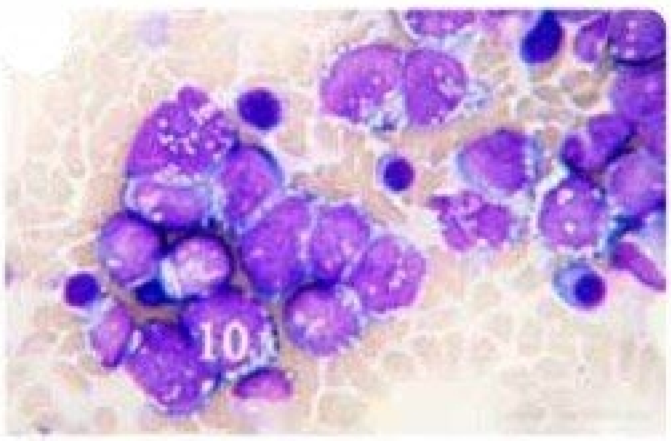
- Bone Marrow Aspirate



[redacted]

BURKITT'S LYMPHOMA
A tumor of the jaw (most common site) distorts the child's face.

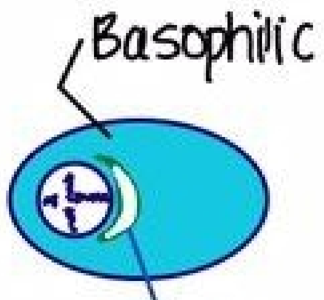
- Immunophenotype
  - B cell CD10 +
    CD19 +
  - Germinal Center } BCL-6 +
- Cytogenetics : t(8:14) : MC
  t(8:22)
  t(2:8)
  Chromose 8 → C-MYC Translocation
- Poor prognosis but chemosensitive



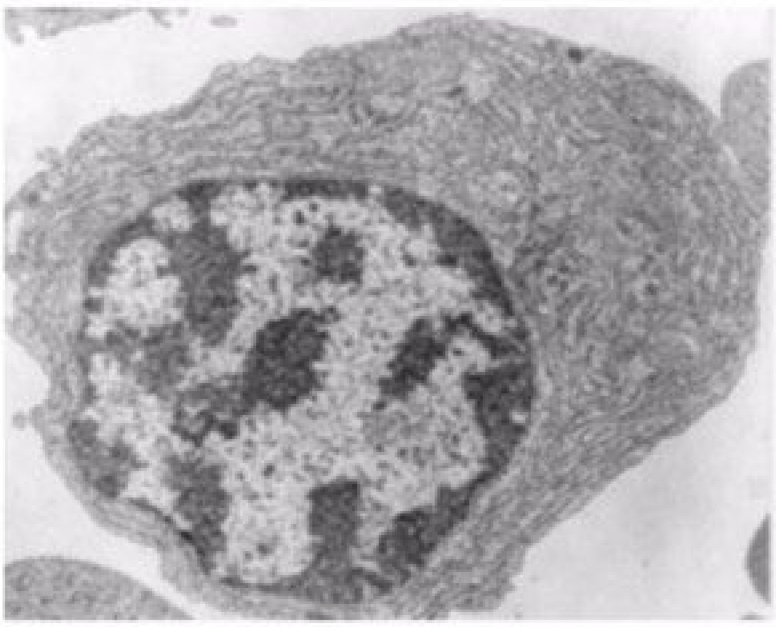
BURKITT'S LYMPHOMA
Bone marrow aspirate smear showing typical (royal blue cytoplasm) deeply basophilic cytoplasm and numerous lipid vacuoles

PLASMA CELL DISORDERS

- Normal : • Small round oval cell
  • eccentric nucleus
  • radially arranged chromatin
    ↓
    Cartwheel appearance
  • Basophilic (d/t ↑ ER)

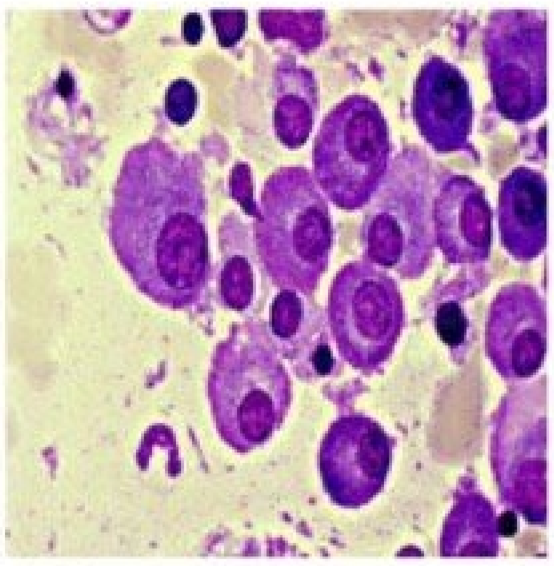


Perinuclear Hoff : d/t Golgi bodies



PLASMA CELL

Electron microscopy showing prominent cytoplasmic rough endoplasmic reticulum. The nucleus has radially arranged clumps of chromatin (Cartwheel or clock face pattern).



PLASMA CELL

Plasma cells have an eccentric nucleus with a clock-face or cartwheel chromatin pattern, a perinuclear clear area (Hof area) corresponding to the Golgi apparatus, and a basophilic cytoplasm due to rough endoplasmic reticulum (rER) for protein synthesis.

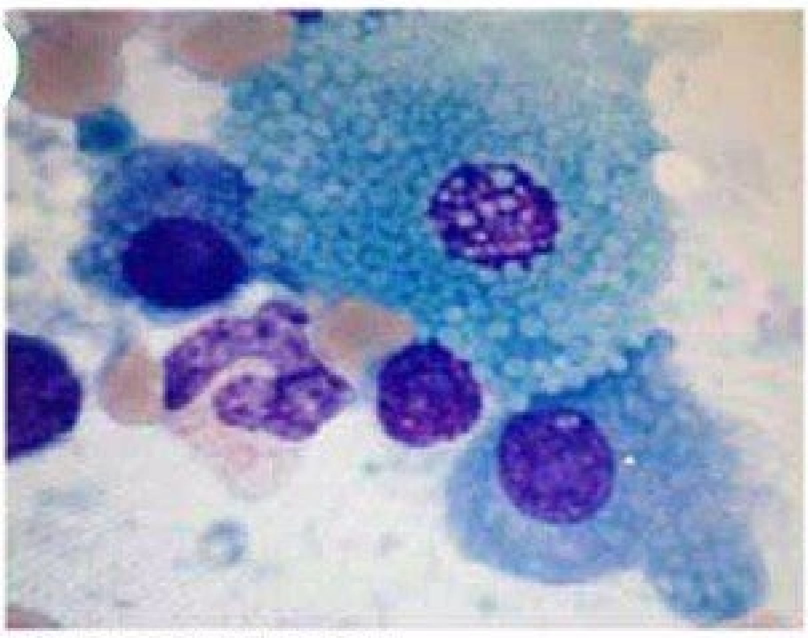
Abnormal plasma cell:

i. Hyper chromatic nuclei
ii. No perinuclear huff
iii. More Basophilic

Immunophenotyping

Normal Plasma Cells : CD 38+ | CD 19+
138+ | 20+

Multiple Myeloma Plasma Cells : CD 38+ | CD 19-
138+ | 20-
CD 56+



MULTIPLE MYELOMA

Mott cells are plasma cells with Bluish grape like cluster of cytoplasmic immunoglobulin. Seen in Multiple myeloma.

Monoclona plasma cells ⟶ Abnormal monoclonal ↑ Ig

↓

Such disorders are called Para proteinemia or Dys proteinemia

Eg: • Monoclonal Gammopathy of unknown significance - MGUS
- Smoldering Multiple Myeloma
- Multiple Myeloma
- Walden stom's Macroglobinemia
- Heavy chain disease
  ↑ α-chain : Seligman disease
  ↑ γ chain : Franklin disease.

MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE

- Asymptomatic
- Lab investigation : i. clonal plasma cell <10%
  ii. Serum - M protein <3g/dl
  iii. No evidence of end organ damage
- Risk: Transformation to Smoldering MM

SMOLDERING MULTIPLE MYELOMA

- Lab investigation : i. clonal plasma cell >10%.
  ii. Serum - M protein >3g/dl
  iii. No evidence of end organ damage

MULTIPLE MYELOMA

- Bcell neoplasm forming Abnormal plasma cell under the influence of IL-6
- Abnormal plasma cells release

↓

MIP-1K
(Macrophage Inflammatory-1-Kappa)

↓ ↑ Rank-Ligand expression (in BM stromal cells)
↓
↑ osteoclast
↓
Bone eating
↓
Hypercalcemia

↓ Activation of WNT pathway
↓
inhibit Osteoblast
↓
Osteoblastic activity is measured by Sr. Alkaline phosphatase
↓
∴ here Sr. Alkaline Phosphatase = Ⓝ

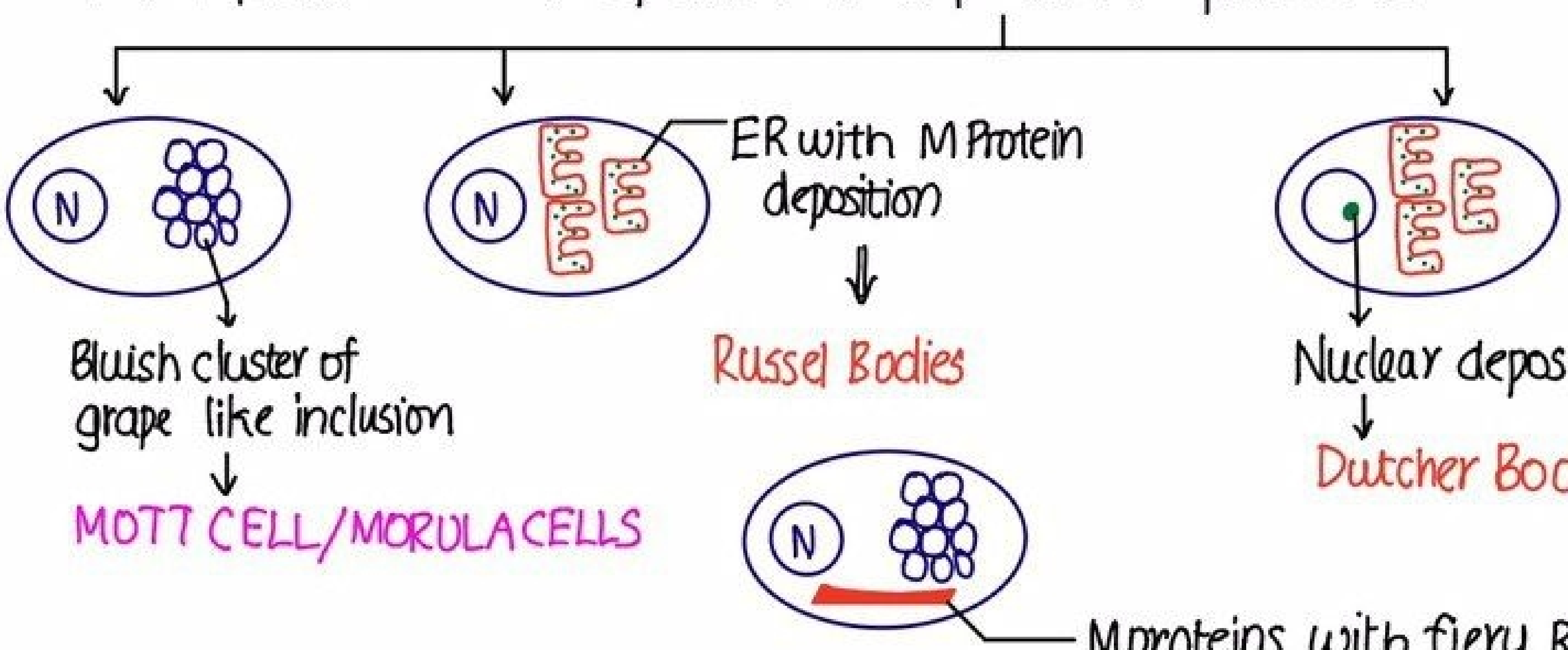
In Fracture of Bone
Brown's Tumor
Paget's diseasease
} ↑ Sr. Alkaline Phosph d/t Activation of Osteoblast

- Clinical Features : • 40-60 yrs old.
  Common presentation: Bone Lytic lesion
  • ↑ monoclonal light chain Ig
  ↓
  ↑ M Proteins
  IgG > A > M > D > E
  IgG ↓ MC
  E ↓ Least common
  ↓
  easily pass through urine
  ↓
  Bence Jones proteinuria (Light chain of Ig)
  Detection : Heat up to 50° → clot
  Heat up to 100° → liquid

- Light chain of Ig deposited in Kidney → AL Type Amyloidosis / Myeloma Kidney
  Primary amyloidosis

- MCC of Renal Failure in MM : Light chain deposition > Hypercalcemia

↑ Mprotein ⟶ ↑deposition of M protein in plasma cell



Bluish cluster of grape like inclusion
↓
MOTT CELL/MORULA CELLS

ER with M Protein deposition
⇓
Russel Bodies

Nuclear deposition of M protein
↓
Dutcher Bodies

Mproteins with fiery Red deposition
↓
FLAME CELL

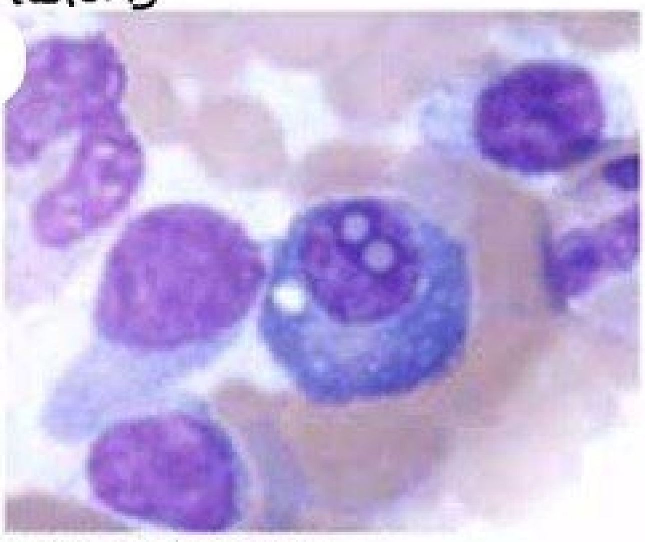
- Diagnostic criteria of MM:

A) Active Multiple myeloma
(>1 criteria +ve)
↓
BM Biopsy showing
Clonal plasma cells >10%
+
Evidence of End organ damage
↓ accessed by
C R A B Criteria
C ↓ Ca^{2+}
R ↓ R.F (Sr.Cr)
A ↓ Anemia
B ↓ Bone Lytic lesion

B) Myeloma defining events
(>1 criteria +ve)
↓
(i) Clonal plasma cell >60%
or
(ii) $\frac{\text{involved light chain}}{\text{uninvolved light chain}} > 100$
or
(iii) MRI ⇒ focal lytic lesions : >5mm in size

- MC Site : Vertebral coloumn
- When it comes to P.B :
Plasma Cell Leukemia
↓
Diagnostic Criteria:
i. Absolute plasma count : $>2\times10^9/L$
(or)
ii) PB: plasma cells : >20%

- Prognostic markers of MM
(i) Best prognostic marker : B_2 macroglobin
  - released by Abnormal P.C
  - ∴ s/o Tumor overload
  - ↑ s/o Bad prognosis



MULTIPLE MYELOMA
Dutcher bodies are intranuclear immunoglobulin inclusions.

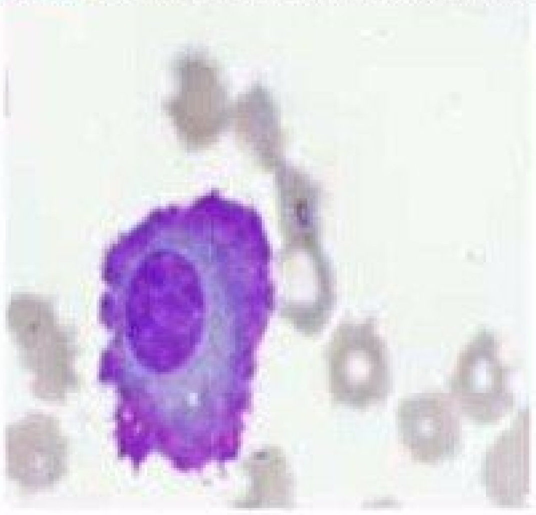


IMAGE: MULTIPLE MYELOMA
Flame cell are plasma cells with red-staining immunoglobulin inclusion material within the cytoplasm.

(ii) Tu. overload markers : i. C- Reactive Protein
ii. Serum LDH
iii. β_2 - microglobin
} if High → Bad prognosis

(iii) Cyclin D_1 ↑↑ : s/o Good prognosis
↓
Best IHC marker of Multiple Myeloma

- MC cytogenetic change : Deletion of 13q → Poor prognosis
- BM Biopsy with Abnormal plasmablast → Bad prognosis

* MCC of death in MM : Recurrent infections

WALDENSTROM'S MACROGLOBULINEMIA

- In tissue/ LN : It's called Lymphoplasmacytoid Lymphoma
- Older , ↑ Monoclonal M protein → ↑↑ IgM
↓
↑ Hyper viscosity
↓
↑ visual impairment
CNS manifestation
- In Lymphoplasmacytoid Lymphoma is a/w MYD-88 acquired mutation.
  - MC Cytogenetic change Chr 6q –
- Heavy chain & Light chain equally affected
↓
No Bone lytic lesion
No Anemia
No Renal Failure
} because all these are d/t light chain

DENDRITIC CELL NEOPLASM

- aka Langerhans Cell Histiocytosis / Histiocytosis –X (Older name)
- Tumor of immature dendritic cell
- Pediatric 2-10 yrs
- Cytogenetics : BRAF mutation
- 4 important variants

1. Letter Siewe
- pediatric < 2yrs
- Aggressive as Multifocal/ Multisystem
- MC presentation : Bone lytic lesion
involve all bones simultaneously!!

2. Eosinophilic Granuloma
- Unifocal / Multifocal
- Unisystem
- MC Presentation : Calvarial defect/ Scalp defect

3. Hand Schuller Christian disease.
- Triad presentation
  i. Diabetes insipidus
  ii. Calvarial deposit
  iii. Ex-ophthalmus

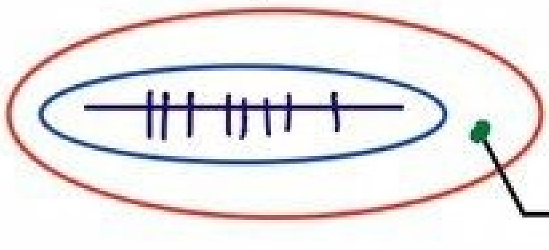
4. Pulmonary LCH
- seen in smokers
- considered as neoplasm d/t BRAF mutation.

- shows symptoms of Seborrheic dermatitis like lesion (bcoz tumor cell infiltarating skin)

- Investigation for LCH :

Immunophenotyping :
- CD 1a (Best marker)
- S-100 , HLA-DR
- CD 207 (=Langerin protein)

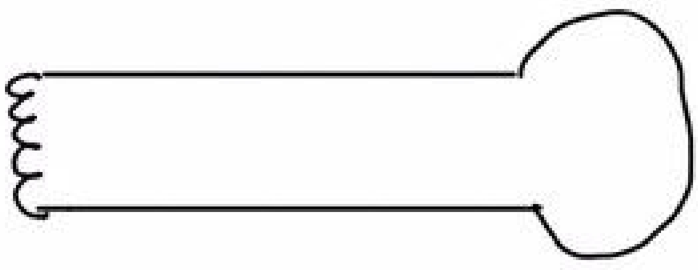
M/E : Langerhan cell



- Round oval cells
- Elongated Nucleus with grooving (= Coffee Bean appearance)

→ Birbeck granules made up of Langerin protein)

↓



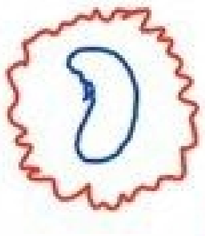
Confirmed by EM
Pentalaminar Rod like structure with dialated terminal ends
(Tennis Racket appearance)

Tennis Racket cell : In Rhabdomyoblast in RMS

Gonadal involvement is absent in LCH

HAIRY CELL LEUKEMIA

- Rare neoplasm
- B Cell type
- MC presentation : Massive Splenomegaly
- Peripheral Smear :
  - Reniform nucleus
  - Hairy projection : Cytoplasmic projection



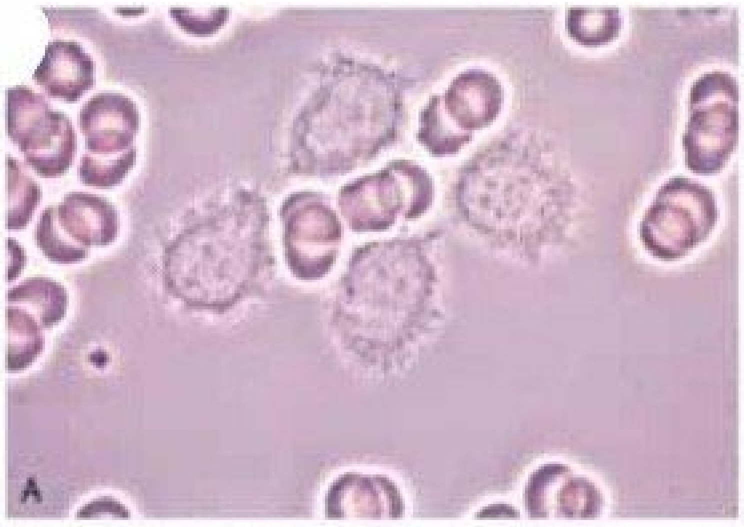
Best visualised : Phase contrast microscopy

- Cytochemical Staining : TRAP +ve (Tartarate Resistant Acid Phosphatase)
- BM aspirate : Dry tap (No tum. cells coming out)

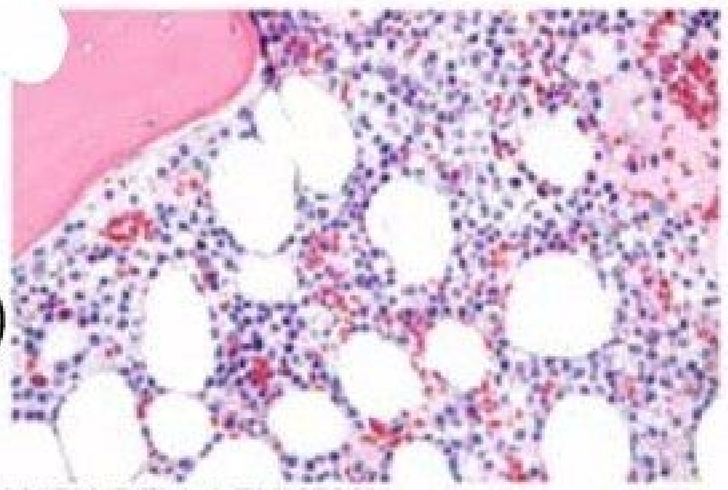
↓

d/t Perisinusoidal Fibrosis
(Hairy cell → release Fibrogenic Cytokine → Fibrosis)

Note : BM is HYPERCELLULAR



HAIRY CELL LEUKEMIA
Hairy cell (B-cells) best detected by phase-contrast microscopy. CD markers are 11c, 25, 103+ve. Most specific marker is Annexin A1.



HAIRY CELL LEUKEMIA
Biopsy shows clusters of monotonous appearing hairy cells adjoining blood lakes. Neoplastic cells have uniform round or oval nuclei, inconspicuous nucleoli and abundant clear cytoplasm surrounding the nucleus creating a fried-egg appearance.

- BM Biopsy : i. Hypercellular BM
  ii. Honey comb appearance : Tumor cell arrangement pattern
  iii. Fried Egg Tu. cell : d/t perinuclear clearing

- Immunophenotyping : • CD 11C • CD103
  • CD 25 • Annexin A-1
- Cytogenetics : >90% of HCL +ve for BRAF mutation
- EM : Ribosomal Lamellar complexes.
- C/f : Monocytopenia
  ↓
  ∴ ↑ Risk of Atypical TB
  a/w Polyarteritis Nodosa.

DIFFUSE LARGE B CELL LYMPHOMA

- B Cell type
- Older age group M>F
- Age : 60 yrs +
- MC Type of NHL
- Worse prognosis
- C/f :

DLBL

→ Immodeficiency associated
- a/w i. HIV
  ii. BM tumor

→ Primary Effusion Lymphoma
- older individual
- Malignant pleural effusion
  Malignant Ascites
  Body cavity involving Lymphoma
- a/w HHV 8

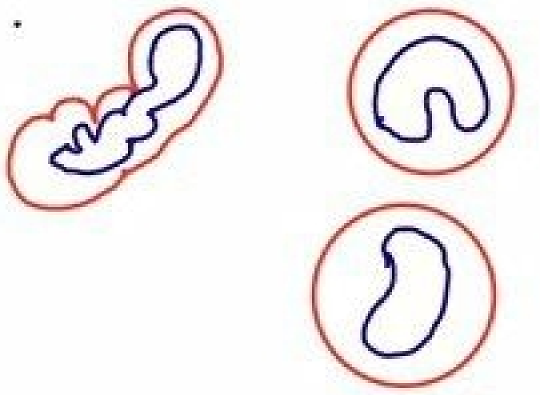
- Immunophenotyping : CD 19 +ve | CD 10 & BCL-6
  CD 20 +ve | variably +ve

- Cytogenetics : # t(14:18)
  # BCL-6 Dysregulation/ translocation
  # MYC over expression

ANAPLASTIC LARGE CELL LYMPHOMA

- T cell type of Lymphoma , Good prognosis
- Young adults
- d/t Chromosomal re-arrangement of ALK gene (Chr. 2)

* LN Biopsy :



Embryo like
Kidney like/Reniform } Nucleus
Horse shoe like
⇓
called as Hallmark cell

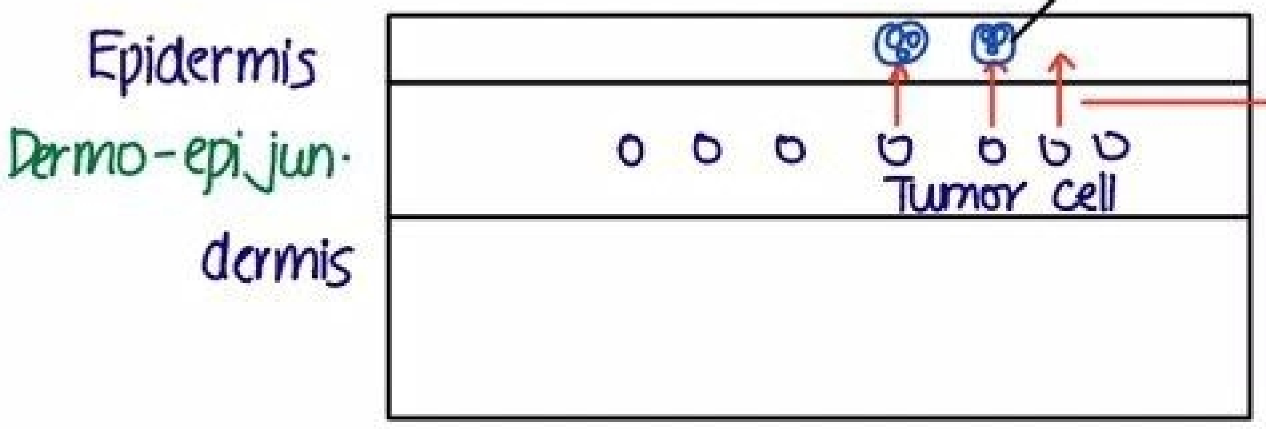
MYCOSIS FUNGOIDES

- Tcell lymphoma (CD4 T cell : Neoplastic cells)
- In skin called as Mycosis Fungoides
  In P.B called as Sezary Leukemia

- Skin showing : Fungus like infection

↓

Skin Biopsy



Pautrier's Micro abscess
⇑
In epidermis they form small abscess

Epidermotropism : movement of tu. cells from Dermo epidermal junction to Epidermis

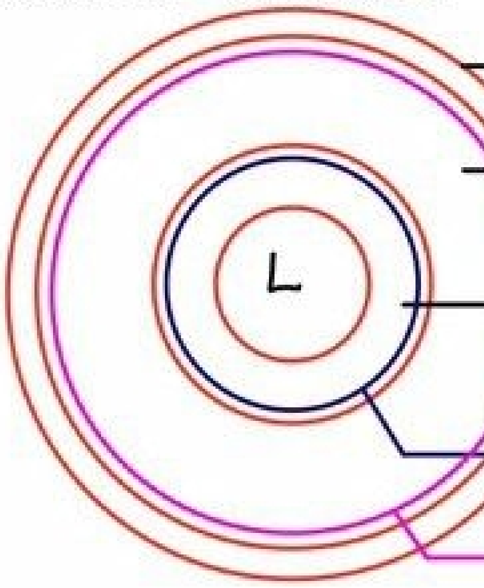
- When the patient is having generalised Erythoderma
  ⇓
  Tumor cells are involving P.B
  ⇓
  Sezary's Leukemia
- Peripheral smear shows Cerebriform Nucleus
  such cells are called as Sezary Lutzner Cell

Sezary Lutzner Cell

poor prognosis d/t freequent recurrence after Chemotherapy

BLOOD VESSELS AND CVS

BLOOD VESSELS



Tunica adventia : Collagen & elastic tissue
Tunica media : Smooth muscle & elastin
Tunica intima : 1-2 layers of endothelial lining
Internal Elastic Lamina : seperate intima & media
External Elastic lamina : seperate media & adventia

VASCULITIS

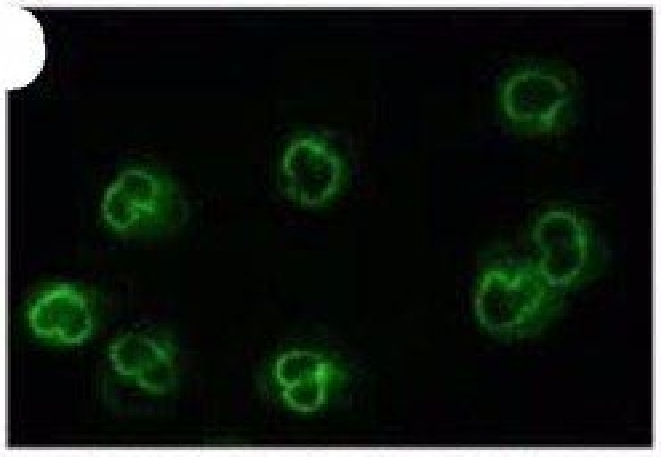
- Inflammation of blood vessel
- a/w ANCA (Anti neutrophilic cytoplasmic Ab)

p-ANCA
(perinuclear)

Target MPO

Indirect immuno flourescence

Seen in :
Microscopic Poly angitis
Churg-strauss Syndrome
Good pasteur



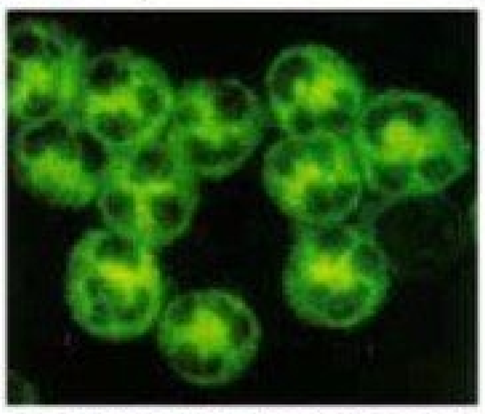
P-ANCA BY INDIRECT IMMUNOFLUORESCENCE
Showing heavy staining in perinuclear area and non-reactive cytoplasm

C-ANCA
(cytoplasmic)

Ab against proteinase

Indirect immuno flourescence

Seen in :
Wegner's Granulomatosis
↓
C-ANCA in 75%
p-ANCA in 25%



C-ANCA BY INDIRECT IMMUNOFLUORESCENCE
Showing heavy staining in cytoplasmic area while multilobulated nuclei (clear zones) are non-reactive

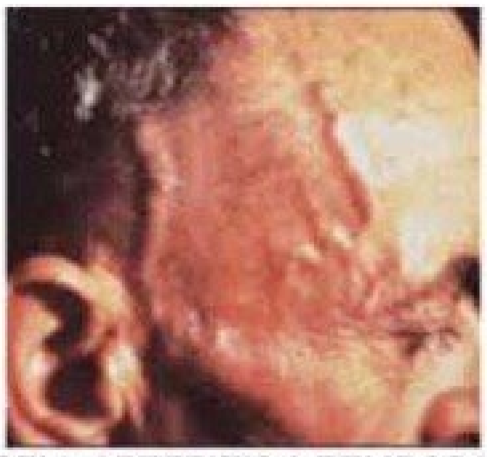
a-ANCA
(both p+c)

Present in :
i) Autoimmune Hepatitis
ii) Inflammatory Bowel Disease
iii) Rheumatoid arthritis

CLASSIFICATION OF VASCULITIS

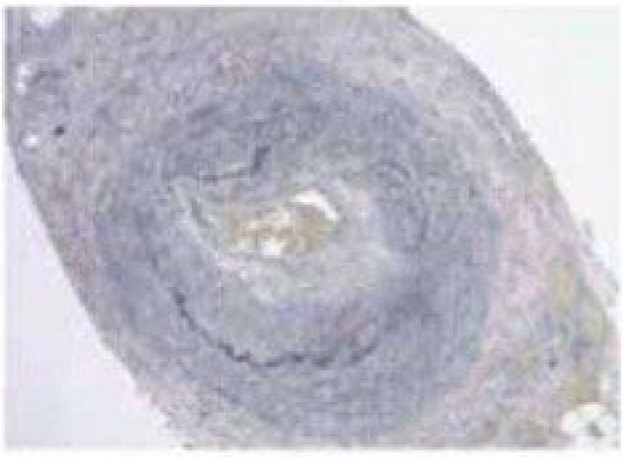
Large Vessel Vasculitis	Medium Vessel Vasculitis	Small Vessel vasculitis
i) Temporal arteritis (Giant cell arteritis)	i) Poly arteritis Nodosa (PAN)	i) Wegnern's granulomatis
ii) Takayasu arteritis	ii) Kawasaky-disease	ii) Microscopic polyangiopathy
	iii) Thromboangitis obliterans Beurger's disease	iii) Churg-strauss synd.

Giant Cell Arteritis

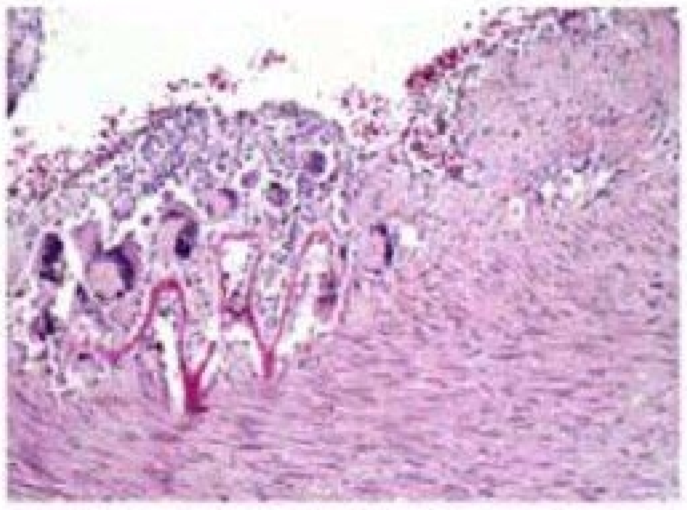


GIANT CELL ARTERITIS (=TEMPORAL ARTERITIS
Temporal artery of a patient with classic giant cell arteritis shows a thickened, nodular, and tender segment of a vessel on the surface of head.

- aka Temporal arteritis
- Female >50yrs
- C/f : * MC presentation Unilateral Temporal Headache
  (MC Site : Superficial Temporal artery)
  * Most specific presentation : Jaw claudication
  * Joint pain & arthritis
  * Joint pain /stiffness of Neck, Shoulder or Hip girdle
  ↓
  called as Poly myalgia Rheumatica
- MC vasculitis :
  Adults : Giant cell arteritis > Cut. vasculitis
  Pediatric : Henoch Scholein purpura > Kawasaki disease
- Lab finding :
  i) Normocytic Normochromic anemia
  ii) ↑ ESR
- Gross : Temporal area with dialated & tortous segmental nodular thickenning of temporal artery
- M/E : Segmental biopsy of superficial temporal artery
  Optimum Length : 3-5cm
  i) Granuloma present
  ii) Multinucleated giant cell
  iii) Fragmentation of internal Elastic lamina



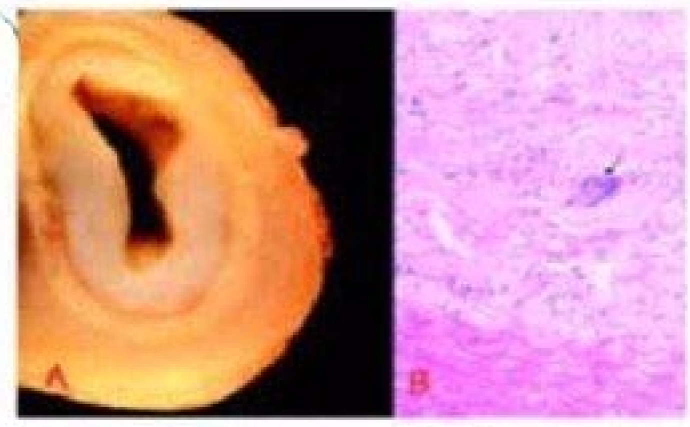
GIANT CELL ARTERITIS (=TEMPORAL ARTERITIS)
Verhoeff-Van Gieson staining (an elastic stain) shows the fragmentation, distortion and lack of continuity of the internal elastic lamina, a characteristic feature of temporal arteritis.



GIANT CELL ARTERITIS (=TEMPORAL ARTERITIS)
Hematoxylin and eosin stain of section of temporal artery showing giant cells at the degenerated internal elastic lamina in active arteritis.

Takayasu Arteritis

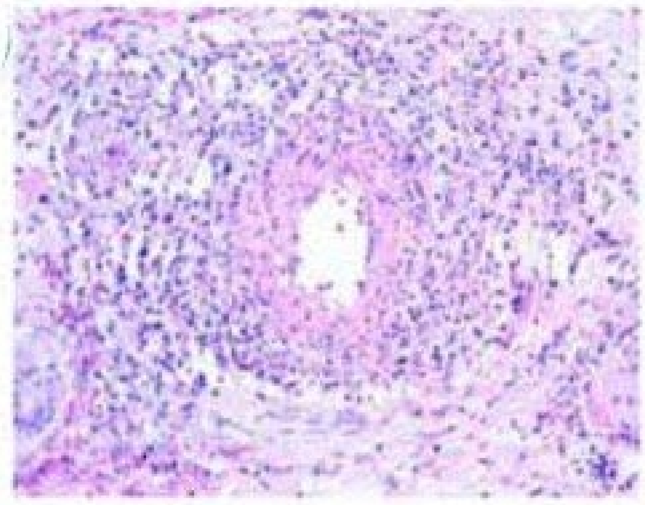
- aka Aortic arch syndrome, Pulseless disease
- Granulomatous inflammmation of aortic arch
- MC Site : Subclavian artery
- Female <40 yrs
- MC presentation : pulse weaker in upper extremity
- Lab finding:
    - i) Normocytic Normochromic anemia
    - ii) ↑ ESR
- Gross : i) T. intima narrow & degenerated
    - ↓
    - ii) d/t Tunica media Thickenning
    - iii) Fibrosis in Tunica adventia
- M/E : i) Dense inflammation with granuloma
    - ii) Multinucleated giant cells



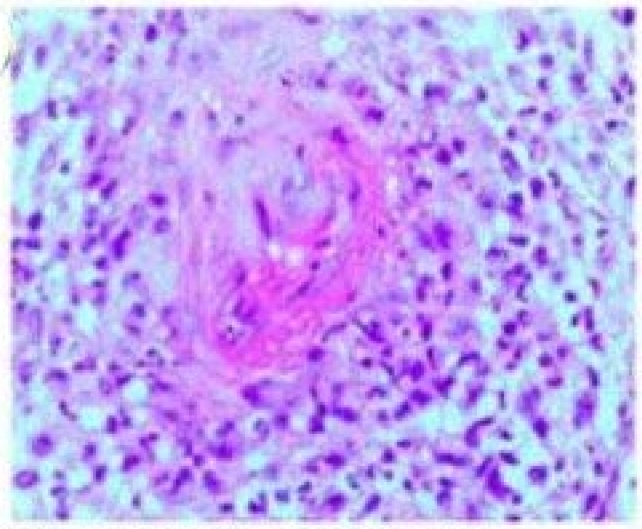
TAKAYASU ARTERITIS.
A) Gross specimen is showing extensive intimal thickening with attenuation of the media and adventitial fibrosis.
B) Microscopy reveals degeneration of the media with a dense inflammatory infiltrate, including giant cells (arrow).

Poly arteritis Nodosa (PAN)

- Immune complex mediated vasculitis
- Young Males
- 30% of PAN case a/w Hepatitis B inf.
    also a/w Hairy Cell Leukemia
- C/f : Fever
    - Weight loss
    - Neurological involvement
    - Renal & visceral arteries are effected
    - Pulmonary arteries spared
- Lab finding : i) No ANCA
- M/E : i) Necrotising transmural inflammation
    - # all stages of inflammation seen
    - i.e acute & chronic inflammation
    - ↓ ↓
    - N° & Lymphocyte infiltaration
    - ii) Fibrinoid Necrosis.



POLYARTERITIS NODOSA (PAN)
Transmural inflammation and fibrinoid necrosis of blood vessel.



POLYARTERITIS NODOSA (PAN)
Transmural inflammation and fibrinoid necrosis of blood vessel.

Kawasaki Disease

- aka Mucocutaneous Lymph Node Syndrome
- Pediatric vasculitis seen in <4yrs of age
- Mucous membrane & Skin } inflammation
- Diagnosis : Fever in Children will have RASH

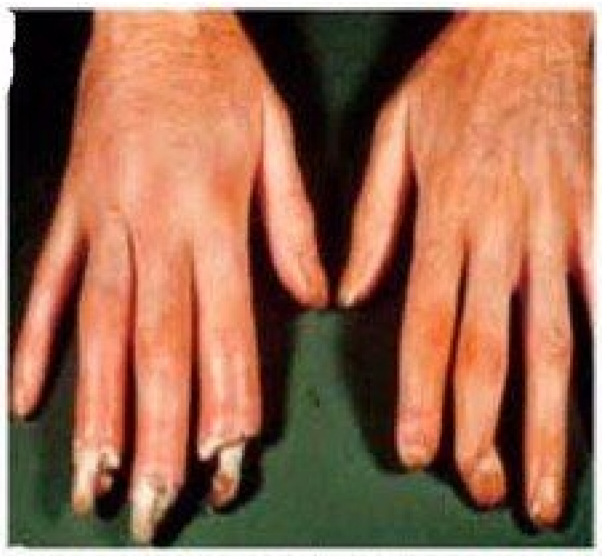
⇒ Fever for >5days
+
any 4 of the following 5

i) Conjunctivitis (B/L Nonsuppurative)
ii) Rash (Polymorphous to desquamative)
iii) Adenopathy (LN Enlargement)
iv) Strawberry Tongue : Oral mucositis
v) Hand Foot involvement : Edema & Erythema

⇒ Fever + 3/5 + Evidence of coronary artery disease by 2D Echo or coronary angiography

- Lab findings : anti-endothelial Ab present
- MCC of death : Coronary Artery disease

Thromboangitis Obliterans



THROMBOANGIITIS OBLITERANS (TAO)

TAO and involvement of the hands. Necrosis of the distal part of the fingers due to ischemic damage.

- aka Beurger's disease
- Young u 35yrs+
- h/o Heavy smokers
- Early manifestation : Raynaud's phenomenon
- C/f : • Intermittent claudication (Intermittent pain relieved by rest)
  - • Neural involvement : persistent pain even at rest
- MIE : • Thrombi with Neutrophilic micro abscess obliterating artery } Intermittent claudication

↓

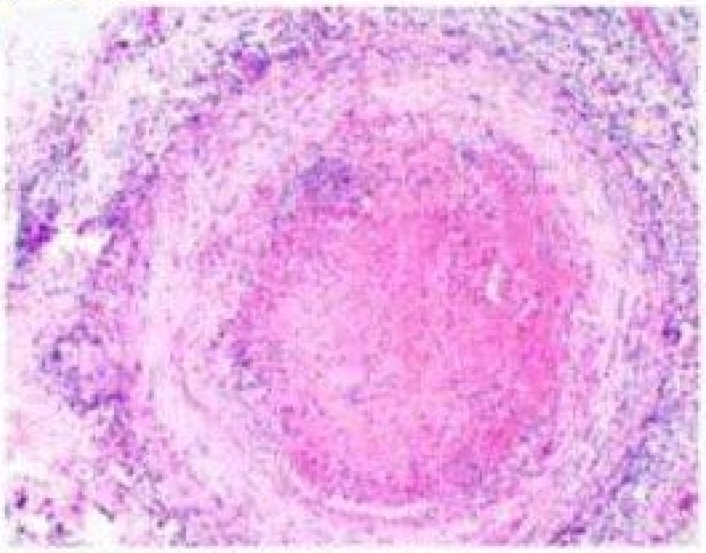
Thrombi involving vein

↓

Thrombi involving nerve } Pain at rest also

↓

Necrosis → Autoamputation of tip of fingers

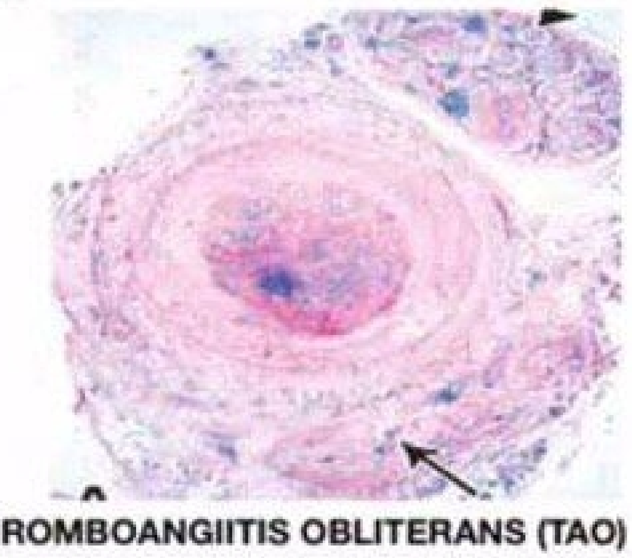


THROMBOANGIITIS OBLITERANS (TAO)

Showing Segmental thrombosing vasculitis with microabscess.

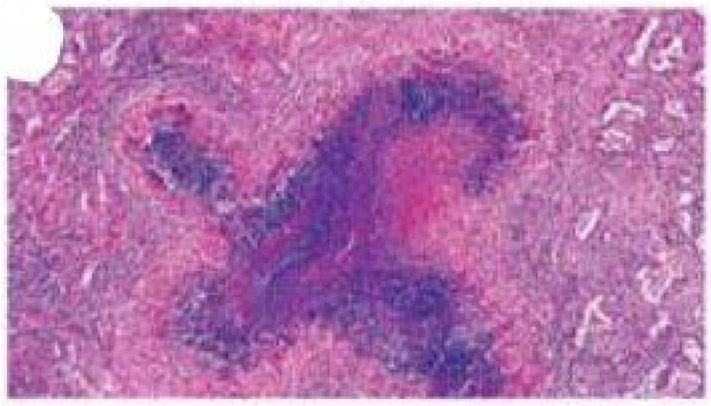
Wegner's Granulomatis

- New name : Granulomatosis with polyangitis
- Necrotising vasculitis of small blood vessals
- Triads : i) Necrotising Granulomatous Vasculitis
  - ii) Necrotising Granulomatous lesion of Resp tract (both upper & lower)
  - iii) Necrotising Glomerulo nephritis
- MIE : • Necrosis "Geographical" ∵ of serpentine borders
  - • Granuloma & Multi nucleated giant cell



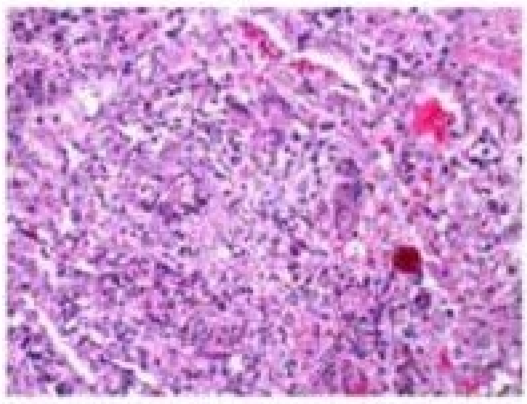
THROMBOANGIITIS OBLITERANS (TAO)

Showing segmental thrombosing vasculitis involving vein, artery, and nerves



GRANULOMATOSIS WITH POLYANGIITIS (FORMERLY WEGENER GRANULOMATOSIS)

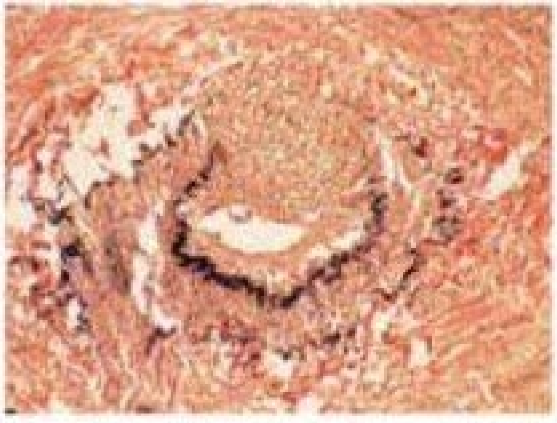
This large area of necrosis has a "geographical" pattern with serpiginous borders and a basophilic center.



GRANULOMATOSIS WITH POLYANGIITIS (FORMERLY WEGENER GRANULOMATOSIS).

There are chronic inflammatory cells and giant cells including Langhans giant cells in the biopsy.

- On Elastic stain i) Damage / Rupture of both internal & external elastic lamina
- C/f :
  - * 40yrs +
  - * Triads :
    - a) Necrotising vasculitis
    - b) Cough, dyspnea, Hemptysis (LRT)
      Otitis media, rupture of nasal septum
      Chronic sinusitis (URT)
    - c) Kidney : Crescentric GN
      - Hematuria
      - RBC casts
- Lab finding : * C-ANCA 75% cases
  p-ANCA 25% cases



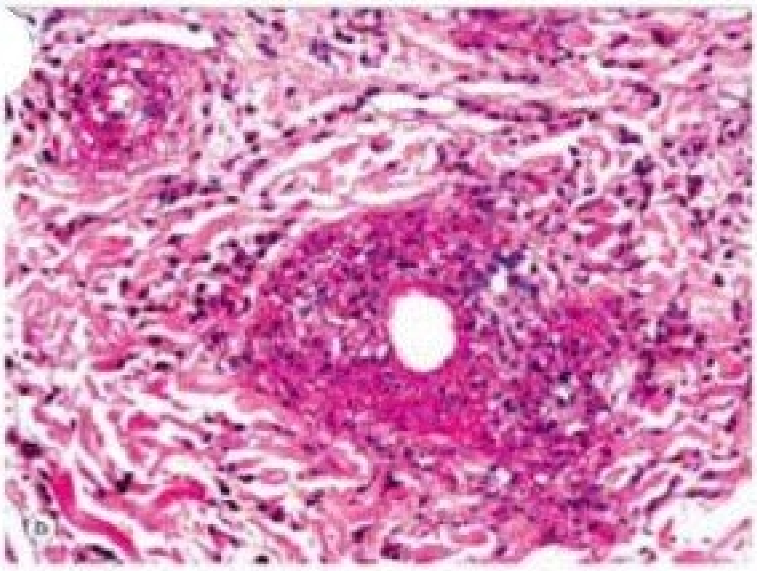
GRANULOMATOSIS WITH POLYANGIITIS (FORMERLY WEGENER GRANULOMATOSIS). Vasculitis in this artery is characterized by a focal, eccentric, transmural chronic inflammatory infiltrate that destroys the inner and outer elastic laminae (elastic stain).

Microscopic Polyangitis

- aka Microscopic PAN
-

PAN	microscopic PAN
* p-ANCA -ve * medium vessel vasculitis	* p-ANCA +ve * small vessel vasculitis

- M/E : i) Fibrinoid necrosis
  ii) Nuclear fragmentation / Nuclear dust present on Blood vessel wall
  ↓
  ∴ aka Leukocytoclastic Vasculitis
  iii) No granuloma
- C/f : • Cough hemoptysis
  • Hematuria



LEUKOCYTOCLASTIC VASCULITIS Showing perivascular leukocytoclasis (destroyed leukocytes as nuclear dust).

Wegner's Granulo.	Microscopic PAN
* CANCA +ve	* p-ANCA +ve
* Granuloma ⊕	* No granuloma
* Nasopharyngeal involvement	* Nasopharyngeal involvement ⊖

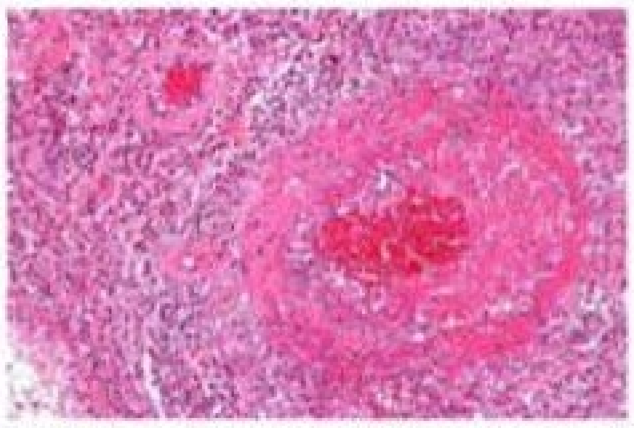
Henoch-Schonlein Purpura

- aka Anaphylactoid purpura
- MC vasculitis in children
- These are because of IgA deposits with in small vessels
- C/f : Triad
  - G : Glomerulonephritis (RPGN)
  - A : Arthralgia / Abd. pain
  - P : Palpable purpura
    ↳ Not a/w Platelet count ; a/w IgA complex causing vasculitis

- Renal involvement : seen in 30% cases of HSP
- Lab diagnosis : i) Thrombocytosis
  ii) ↑ IgA level inserum
  iii) Normal C_3 complement

Churg-Strauss Syndrome

- aka Allergic granulomatosis with angitis
- C/f : i) Peripheral eosinophilia
  ii) Allergic asthma
  iii) Allergic Rhinitis
  } small vessel vasculitis
- similar features of PAN



ALLERGIC GRANULOMATOSIS WITH POLYANGIITIS (FORMERLY CHURG-STRAUSS SYNDROME).
An artery shows severe vasculitis consisting of a dense infiltrate of chronic inflammatory cells and eosinophils. A necrotic ("allergic") granuloma has a central eosinophilic area of necrosis surrounded by macrophages and giant cells.

PAN	CSS
* No granuloma	* Granuloma
* No eosinophilic infiltarate	* Eosinophilic infiltarates
* No P-ANCA	* P-ANCA ⊕
* Medium Vessel Vasculitis	* Small vessel vasculitis

- Eosinophilic infiltarate in to heart
  ↓
  CHF = MCC of death

Behcet's Disease

- Small vessel vascuitis with neutrophilic vasculitis
- Pathology :

$$T_{H17} \text{ cells} \xrightarrow[22]{IL-17} \text{Neutrophil \& monocytes}$$

↓
causing inflammation & destruction

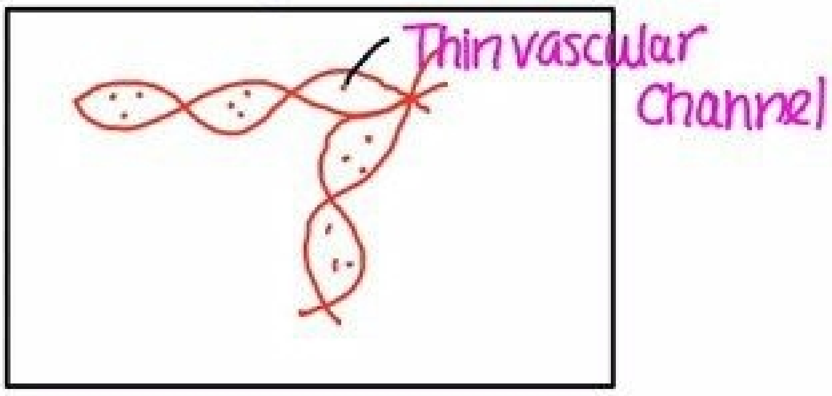
- Presentation Triad :
  i) Recurrent oral arthus ulceration
  ii) Genital Ulcers
  iii) Uveitis
- Anti- endothelial Ab are present against α- Enolase of endothelium

TUMORS OF BLOOD VESSEL

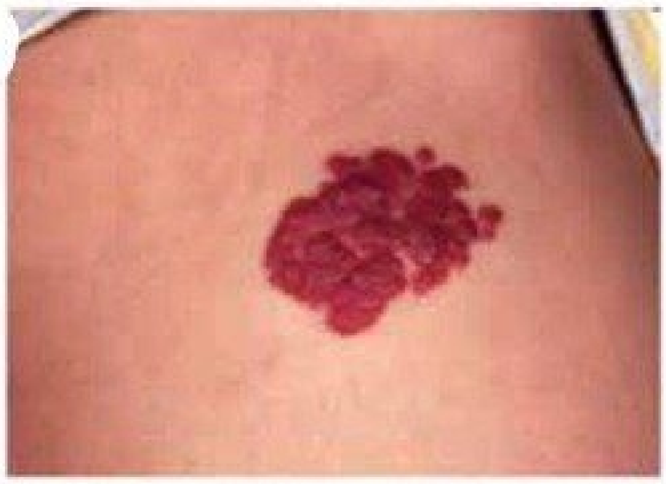
a) Benign	b) Intermediate	c) Malignant
Capillary Hemangioma Cavernous Hemangioma Glomangioma	Kaposi sarcoma	Angiosarcoma

CAPILLARY HEMANGIOMA

- MC type of Benign tumor
- MC site : Skin & mucous membrane
- Gross : Non capsulated
  BV are disorganised
- M/E :

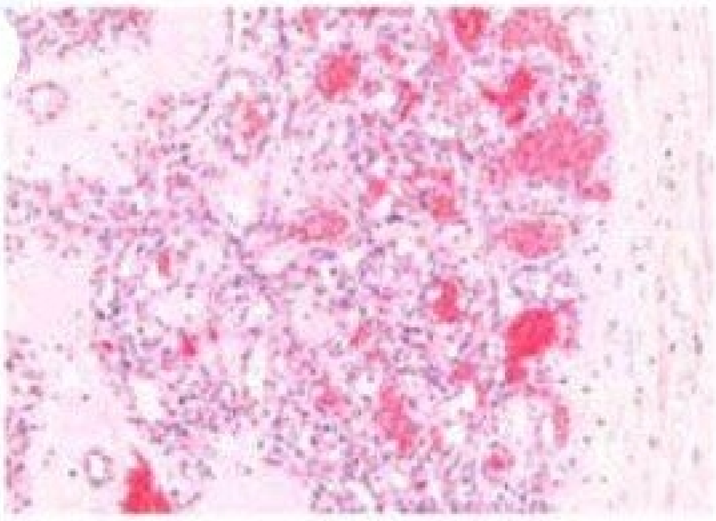


- Strawberry / Juvenile Hemangioma
  - Variant of capillary Hemangioma
  - Start regressing by 1-3 year
  - disappear by 7yrs



STRAWBERRY HEMANGIOMA

Capillary hemangioma red birthmark

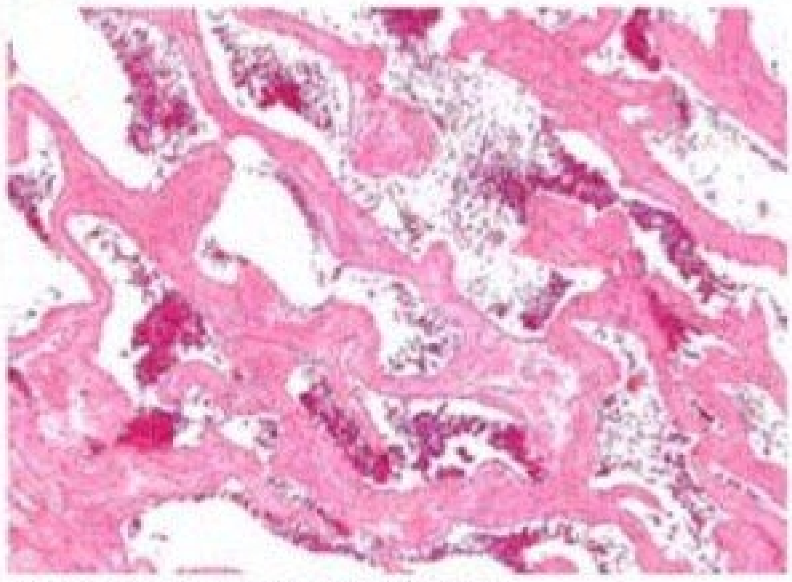


CAPILLARY HEMANGIOMA

Shows thin-walled capillaries filled with red blood cells and scanty stroma.

CAVERNOUS HEMANGIOMA

- Large non-capsulated tumor in
  Skin and Liver (MC Site)
  CNS (a/w VHL syndrome)
- do not regress spontaneously
  These are locally destructive
- M/E : Large vascular channels
  Abundant connective tissue

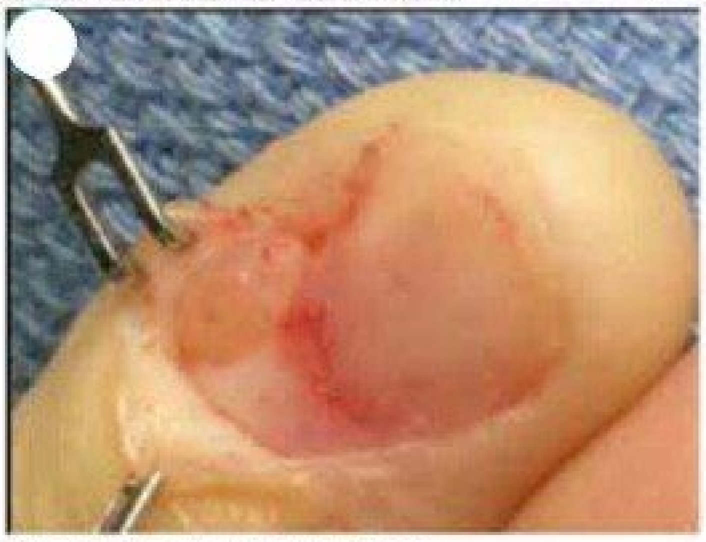


CAVERNOUS HEMANGIOMA

Shows large, dilated cavernous blood-filled vascular spaces separated by connective tissue stroma

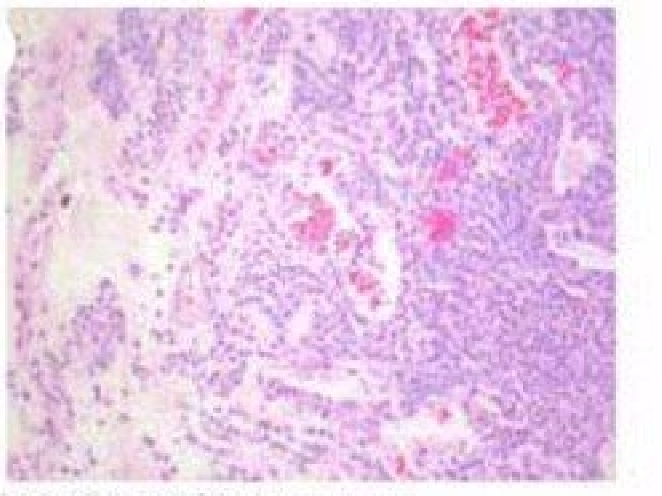
GLOMANGIOMA / GLOMUS TUMOR

- Benig painful tumor
- MC Site : Nail bed (distal phalenges)
- Origin : Smooth muscle of Glomus body
  ↓
  These are specialised arterio venous structure required for thermoregulation
- Gross : Tumor on nail bed
- M/E : i) branching vascular channels
  ii) Round to polygonal cells



GLOMUS TUMOR (GROSS)

Gross shows typical location of tumor under the fingernails.



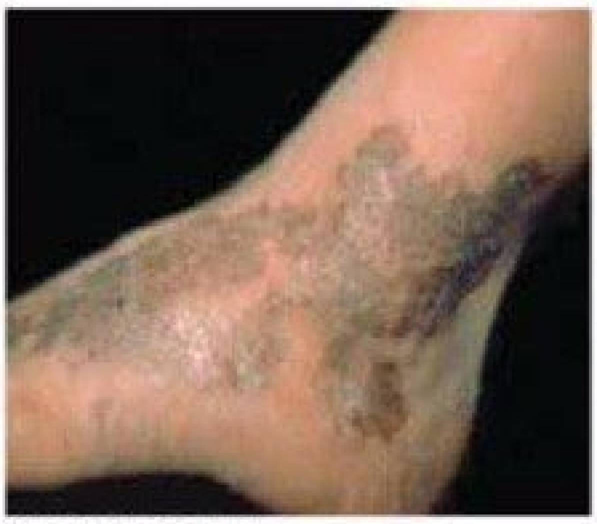
GLOMUS TUMOR (Microscopy)

Microscopy shows two main histologic components consisting of branching vascular channels in a connective tissue stroma and aggregates or nests of specialized glomus cells. Glomus cells are polygonal cells with small and regular regu lar nuclei

KAPOSI SARCOMA

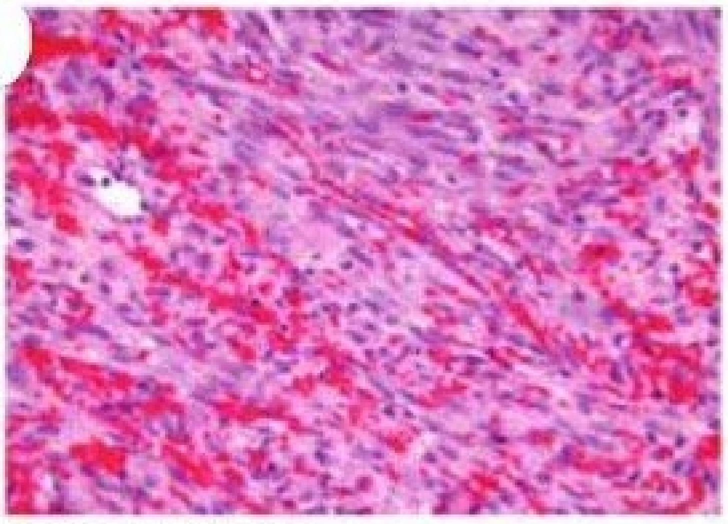
- Intermediate grade
- a/w immunocompromised state
- d/t Human Herpes Virus-8
- MC site : Lower limb skin

- Gross examination:
  - Brownish patch, plaque, Nodular form
- M/E:
  - Proliferating Neoplastic spindle cells & Endothelial cell
  - BV channels with RBC
- Epidemiological classification
  - i) European/Classical
    - Cutaneous/skin lesions very common
    - Not a/w HIV
  - ii) Asian/Lymphadenopathic
    - Not a/w HIV
    - LN Enlargement is common skin rarely effected
  - iii) Transplant a/w
  - iv) HIV a/w



KAPOSI SARCOMA

Classic Kaposi sarcoma usually confined to a small number of lesions on the skin of the lower extremities. Cutaneous lesions are asymptomatic purple, pink, or red macules that may coalesce into blue-violet to black plaques and nodules.

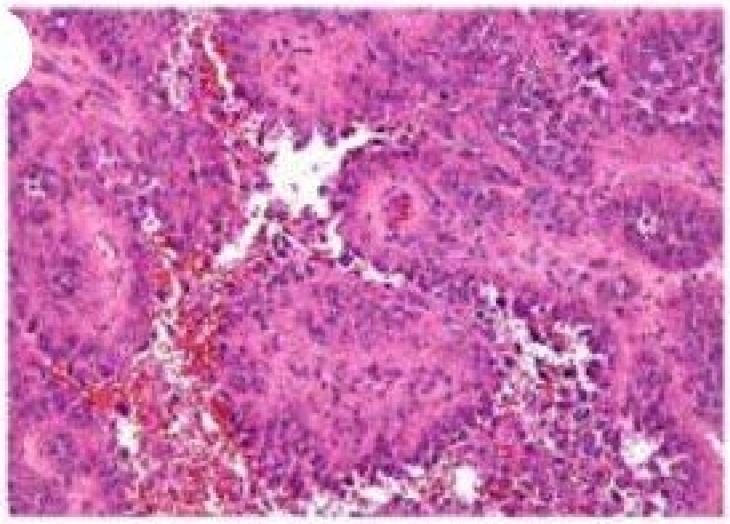


KAPOSI SARCOMA

Numerous poorly differentiated, spindle-shaped neoplastic cells and a vascular channels filled with red blood cells.

ANGIOSARCOMA

- Malignant neoplasm of Endothelial Cells
- Aggressive tumor with poor prognosis
- Etiology : i) Arsenic (Pesticides)
  - ii) PVC (Plastic)
  - iii) Throtrast (Radiologic contrast)
- M/E : i) Atypical Larger endothelial cells
  - ii) Atypical mitotic figures
  - iii) Areas of heamorrhage/necrosis
- IHC : Confirmation CD31 ⊕
  - vWF ⊕



ANGIO SARCOMA

The images show abundant small blood vessels lined by large atypical endothelial cells.

HEART

ARTERIOSCLEROSIS

- thickenning & loss of elasticity of arteries & arterioles

3 TYPES

Arteriosclerosis

i) Benign Hyaline Arteriosclerosis

ii) In Malignant HTN
Hyperplastic arteriosclerosis

Monckeberg Medial Calcific Sclerosis

↓

Tunica media degeneration followed by calcification

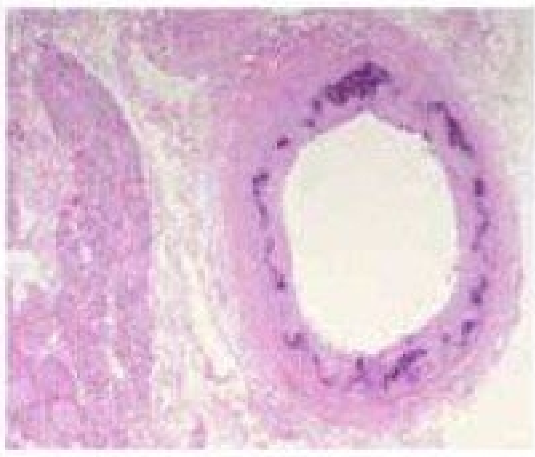
↓

M/E: i) Basophilic Ca^{2+} deposit in Tunica media

- seen in older individual >50yrs
- Non obstructive lesion
  ∴ clinically insignificant

Atherosclerosis

progressive intimal lesions of medium to large artery



MONCKEBERG'S MEDIAL CALCIFIC SCLEROSIS

It is a form of *arteriosclerosis* or vessel hardening where basophilic calcium deposits are found in muscular layer of wall (tunica media).

ATHEROSCLEROSIS

- Etiopathogenesis :

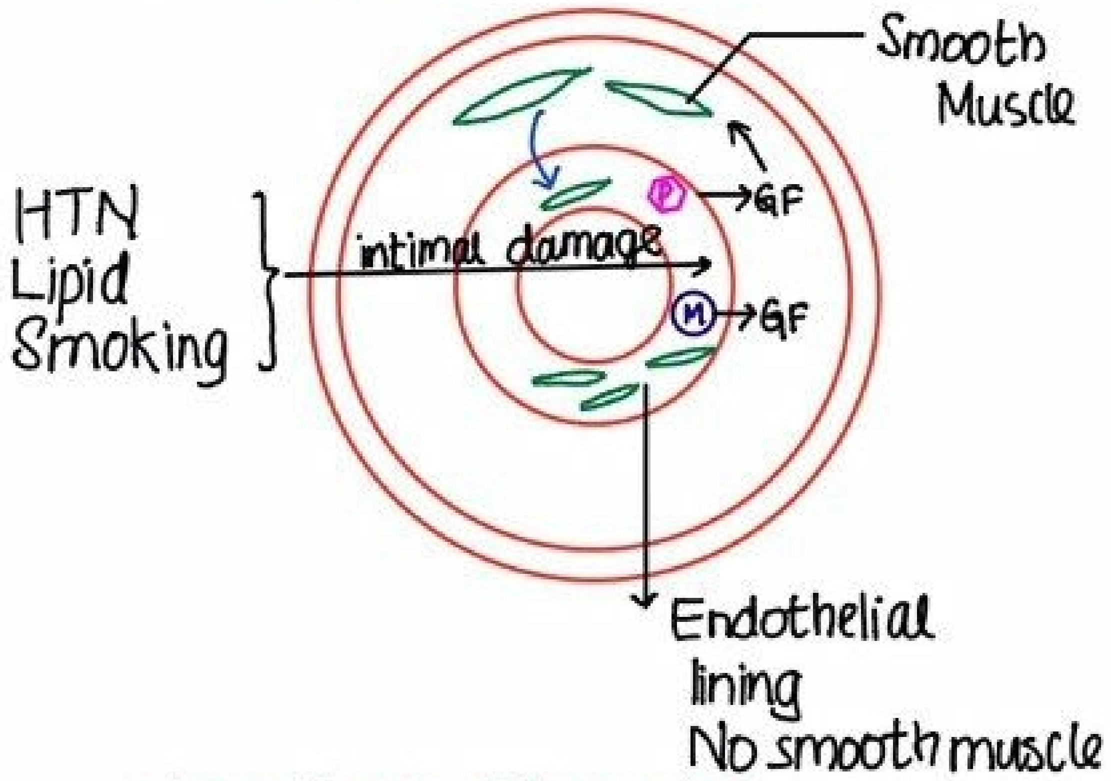
Risk Factors

Modifiable Factors
- obesity
- DM
- Smoking /alcohol
- infections : Herpes virus
  CMV
  Chlamydia

Non-modifiable
- older age
- Male gender
- Stress type A personity
- Hyperhomocyteinemia

- Pathogenesis : Inflammatory response to endothelial injury
  -Most widely accepted Hypothesis

• It's intimal based lesion



Damage of intima
↓
Monocyte interact with platelet.
↓
Growth Factor release into Tunica media
↓
Smooth muscle enters in to Tunica media to tunica intima
(Now Intima with E + SmoothMs)
called Neointima formation
↓
It's a response to vascular inj.
Eg : Infection
Trauma
Grafting

Neo intimal Formation
↓
Macrophage & Smooth musce } phagocytose oxidised LDL

FOAM CELL
⇓
Collection of foam cells in intima form
↓
Atherosclerotic plaque called as
Fatty streaks
↓
Earliest visible vision
⇓
Atherosclerosis

Atherosclerotic plaque contain
i) Fibrous cap
ii) Necrotic core

- MC site for atherosclerosis : Abdominal aorta below renal artery above illeac bifurcation

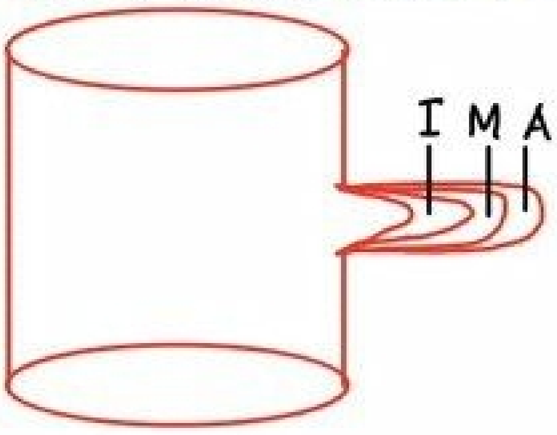
- Least common site : Circle of willis

# Complications : i) Aneurysm
ii) Dissection
iii) Rupture of plaque or thrombi
⇓
CAD/MI

ANEURYSM

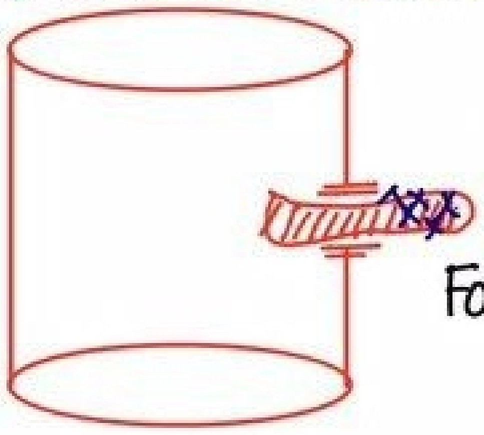
- defined as dialatation of blood vessel wall or wall of heart
- TYPES OF ANEURYSM

a) TRUE ANEURYSM



⇒ All 3 layers are intact
⇒ Seen in
- Atherosclerosis
- Post MI

b) PSEUDO-ANEURYSM

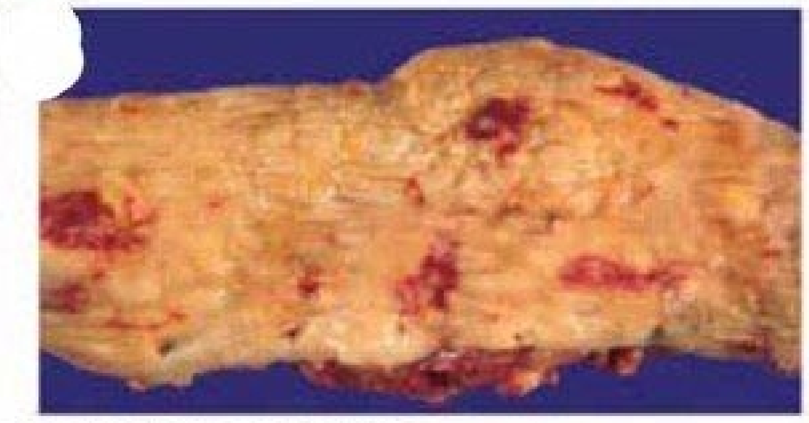


Rupture of BV Wall
↓
Formation of Hematoma
↓
Fibrosis

* No intima, media, adventia
* Fibrous band around Hematoma
* d/t : Post MI Rupture

c) MYCOTIC ANEURYSM

- not a/w Fungal infection
- MCC is staphylococcal inf
↓
damage → dialatation
- MC Site : Femoral artery



SYPHILITIC AORTITIS

inner surface of thoracic aorta is showing the typical "tree bark" appearance due to *intimal wrinkling.*

d) LUETIC ANEURYSM

* aka Syphilitic aneurysm
* encounter in 3° stage of syphilis
* MC Site :
Proximal part of ascending aorta
* Cross section :
i) Wrinkling of aortic wall d/t fibrosis
⇓
TREE BARK APPEARANCE
* Gross Heart :
COR-BOVIUM (Enlarged heart)

d/t Aortic regurgitation leading to enlargement of Left ventricle

AORTIC-DISSECTION

- Dissection of Blood into Tunica media (middle & outer 1/3rd of Tunica media)
- Patient age : 40-60 yrs age
- MCC : HTN

- In younger patient : d/t Cystic medial Necrosis (Tunica media necrosis → Cystic formation)
  ↓
  Seen in: Marfan - syndrome
  Ehler - Danlos Syndrome

CORONARY ARTERY DISEASE / CORONARY HEART DISEASE

- Significant coronary artery obstruction (>75% of CSA of BV)
- It's a spectrum of disease
  - a) **Angina** :
    - it chest pain d/t ischaemia without infarction
  - b) **Myocardial infarction**
    - Ischaemia with necrosis
  - c) **Sudden Death**

MYOCARDIAL INFARCTION

- Ischaemia → Necrosis → Infarction
- MC Blood Vessel involved : Left anterior descending artery
  ↓
  Supplying to i) Apex
  ii) Inter ventricular septum (Ant $2/3^{rd}$)
  iii) Anterior wall of LV
- Least commonly effected : Left circumflex artery
  Supplying : Lateral wall of Left ventricle except for apex

Heart

↓ MYOCARDIUM ↓ PERICARDIUM ↓ ENDOCARDIUM

i) Transmural MI
- all 3 layers Infarction
- ECG : ST wave elevation (STEMI)
- MC pattern of MI

ii) Sub-endocardial infarction
- No-ST-Elevation MI (NSTEMI)

Thrombolytics given (some cases) → Ischaemia Reperfusion injury → MYOCARDIAL STUNNING
↓
poorly contracted Heart

Reason : Because of ischaemi production of FR, Complement, Neutrophil, Ig
↓
Blood supply
↓
FR, Complement, Neutrophil, Ig goes to tissue
↓
More severe damage

Ischaemia Repurfusion injury → Irreversible injury

↓

↑↑↑ Ca^{2+} → Hypertetanic contraction of myocyte

⇓

called as Contraction Band necrosis

MIE : i) Dense, thick irregular wavy eosinophilic structures

Diagnosis MI

: i) ECG : eith ST↑ / no ST↑

ii) Biochemical markers

= Earliest to increase : Myoglobin
- non specific as it release from myocardial injury also
- within 2hr ↑
  within 24hrs : Ⓝ

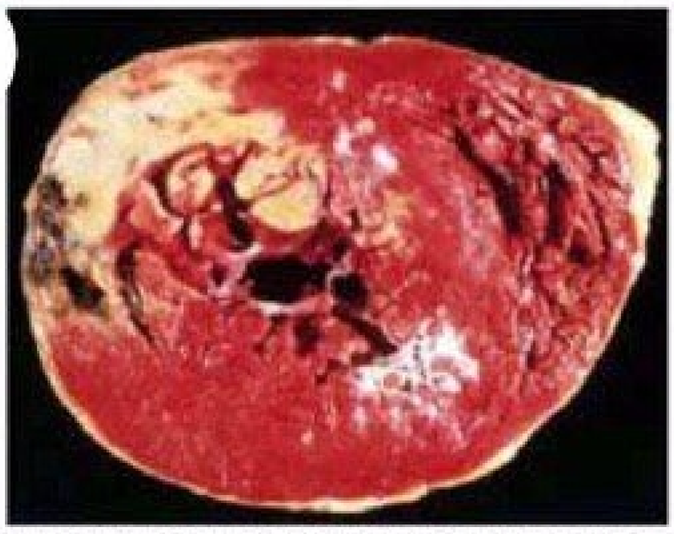
= CK MB : • start : 2-4hrs normal : 2-3days

= Most sensitive / specific : Troponin I > T
BEST
start : 2-4hrs
normal : 7-12days

BEST Marker for RE-INFARCTION : Trop I > CK-MB
⇓
Serial elevation
i.e at the time of admission ⟶ After 3hrs
Increase >20% of initial : s/o Reinfarction

= Serum LDH : • Start : 2-4hrs Normal : 10days
• Flipping of LDH a/w Myocardial Infarction
normally LDH-2 > 1
but after MI LDH-1 > 2

iii) Gross : Autopsy
- Less than 12hrs of MI
TTC Assay : Triphenyl Tetrazolium Chloride



TRIPHENYL TETRAZOLIUM CHLORIDE (TTC) STAIN FOR MI

i) Viable myocardium is red due to preserved lactate dehydrogenase (LDH).

ii) Infarcted areas will be pale due to leakage of LDH.

Normal Tissue
↓
LDH + TTC
↓
Red colour

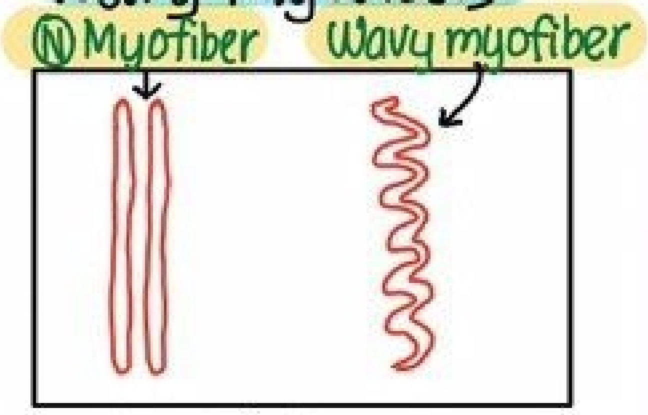
Necrotic Area
↓
Sr. LDH ↑ (as LDH come out from Heart)
↓
Only TTC
↓
Pale colour

- Morphology of MI

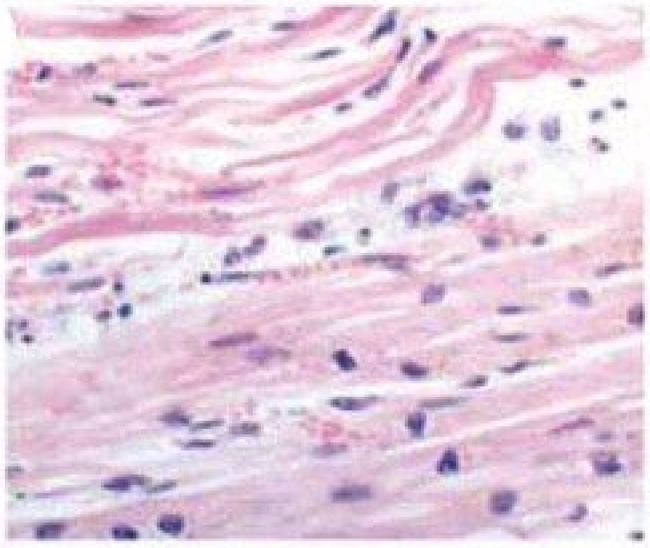
- Gross : Upto 12 hrs - No Grass Features
occasional dark motling
Use : TTC assay

12-24 hrs - Dark motling present
1-3 days - Dark motling + Yellow tan infarct
3-7 days - Dark motling + Yellow tan infarct + Hyperemic Borders
End of 2month - Scarring is completed

- Light microscopy
  Upto ½ hour - No change
  ½ - 4 hour - Wavy myofibers



- earliest light microsopic change



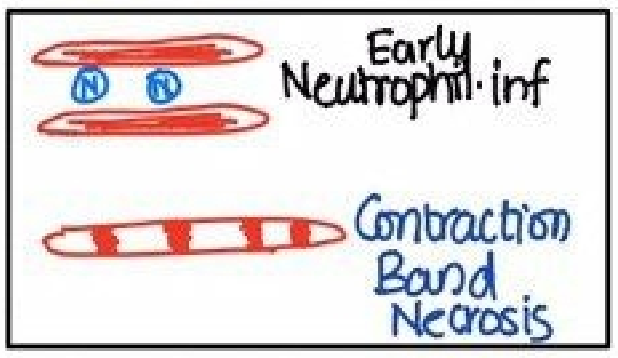
MYOCARDIAL INFARCTION WITH WAVY FIBERS
one day old infarct showing coagulative necrosis and wavy fibers

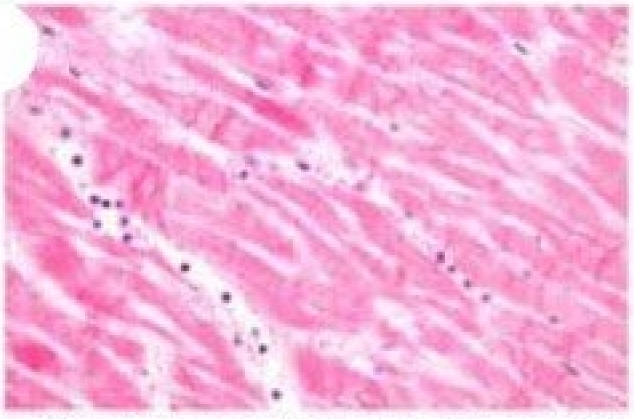
4-12 hrs - Coagulative Necrosis
12-24 hrs - (i) Coagulative Necrosis
- · Architecture : preserved.
- · No nucleus.

(ii) Early N° infiltarates
- · 1-2 neutrophil
- · donot damage myofibers

(iii) Contraction band Necrosis
- · Thick irregular eosinophilic wavy bands

Coag· Necrosis

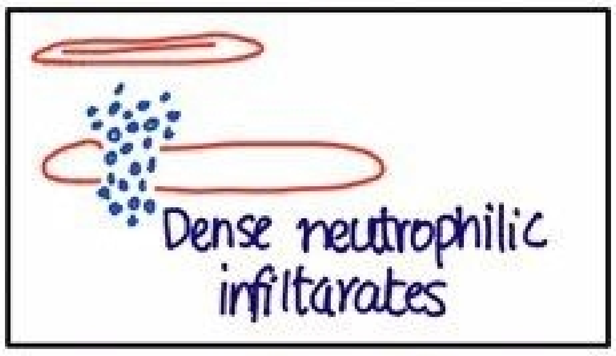


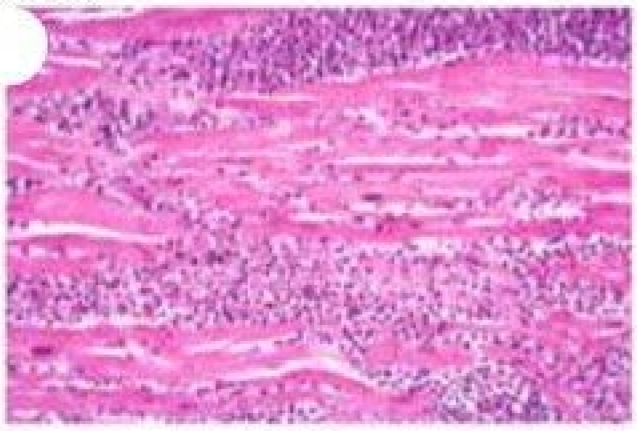


MYOCARDIAL INFARCTION WITH CONTRACTION BAND NECROSIS
Showing prominent, irregular, wavy eosinophilic bands within the myocyte (12 to 24 hours).

1-3 days - Dense neutrophilic infiltarate
· damage surrounding myofibers
- Coagulative Necrosis

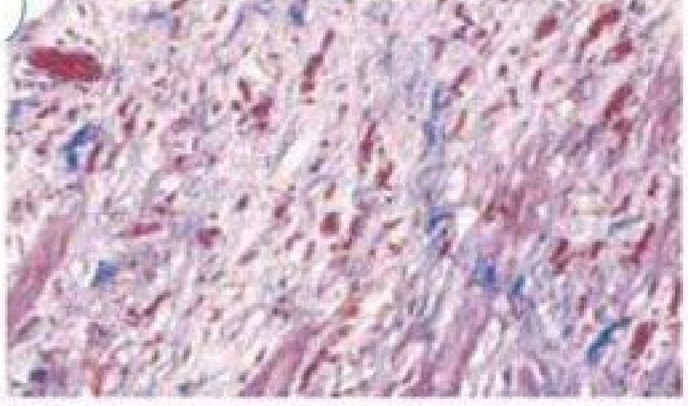
Coag· Necrosis





MYOCARDIAL INFARCTION WITH NEUTROPHIL
Coagulative necrosis which are eosinophilic and devoid of cross-striations and nuclei, with Dense polymorphonuclear leukocytic infiltrate (3 to 4 days old).

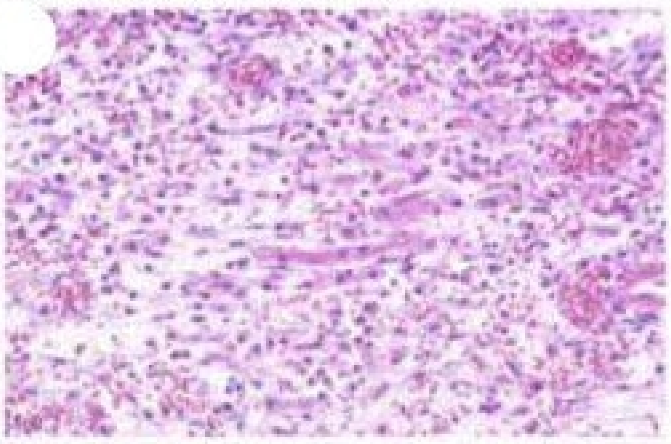
7-10 days - Early granulation tissue
10-14 days - Maximum granulation tissue



MYOCARDIAL INFARCTION WITH GRANULATION TISSUE.
Showing wavy fibrocollagenous tissue and numerous blood filled capillaries (1 to 2 weeks).

By the end of 2month :
Dense collagenous scar

On EM:
i) Within ½ hour :
Mitochondrial swelling
ii) after ½ hour :
Large amorphous densities in Mitochondria



MYOCARDIAL INFARCTION WITH GRANULATION TISSUE.
Showing wavy fibrocollagenous tissue and numerous blood filled capillaries (1 to 2 weeks).

- Complications of MI :
  - i) Arrhythmia
  - ii) Ventricular aneurysm
  - iii) Myocardial Rupture (Free LV wall ; post-MI 2-4 days)
  - iv) Dressler syndrome
    - auto immune disease
    - cause fibrinous pericarditis (post MI)
    - I.P : 1-3 weeks (may be by 1-3days)

RHEUMATIC FEVER & RHEUMATIC HEART DISEASE

- It's an autoimmune disease : F>M
- 10-15yrs more commonly effected
- autoimmune inflammatory disease : caused by Group A β-hemolytic streptococci
  Strains : M-1,3,5,6,18
- It occurs only secondary to sore throat/ pharyngitis and do not due to skin infection (impetigo)

↓ only 3% of case

Rheumatic Heart disease

Pathogenesis : Molecular mimicry / cross-reactivity
- MC valve effected : Mitral valve ; Least common value : Pulmonary valve

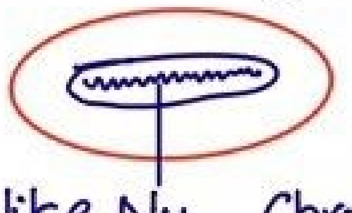
- Morphological Examination

Acute phase

* Aschoff Bodies : Diagnostic of RHD
  These are collection of
  - i) Lymphocyte
  - ii) Plasma cells
  - iii) Swollen collagen myofibers
  - iv) Histiocytes

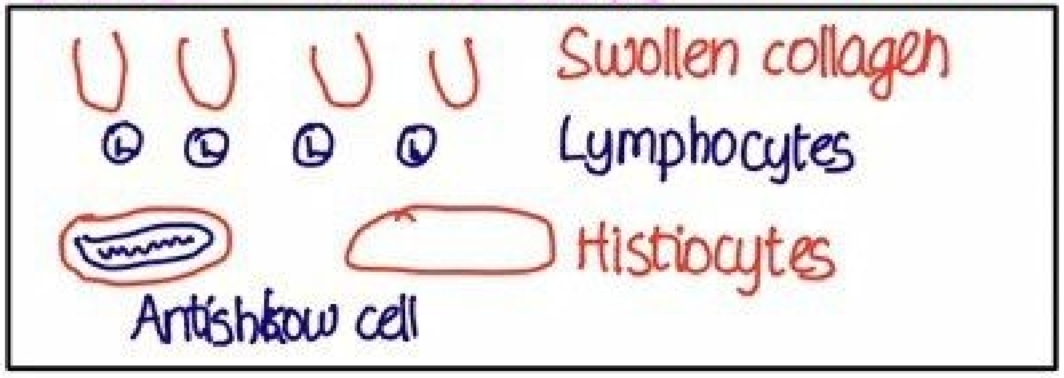
↓

Some showing



Caterpillar like Nu. Chromatin
called as Antischkow cell
(seen in Ⓝ myocardium also)

* seen in all layers of heart
(MC seen in : PERIVASCULAR MYOCARDIUM)



Chronic/healed phase

* Mitral regurgitation

↓

Subendocardial Erosion
at LA post wall

↓

Aschoff Bodies collection

↓

Mc Callum plaques
(MC seen in Chronic RHD)

* Chronicity → Inflammation

↓

Fibrosis & calcification
of valve (Mitral Stenosis)

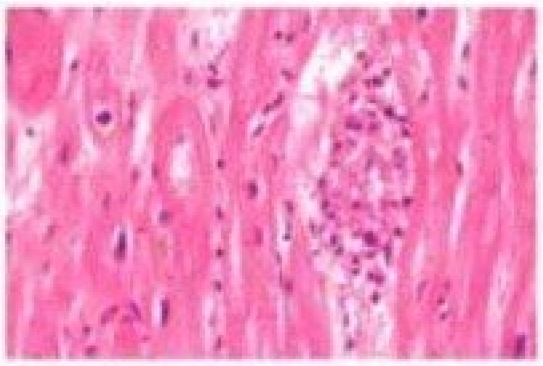
↓

MC valvular defect in Chronic RHD
MC valvular defect in RHD

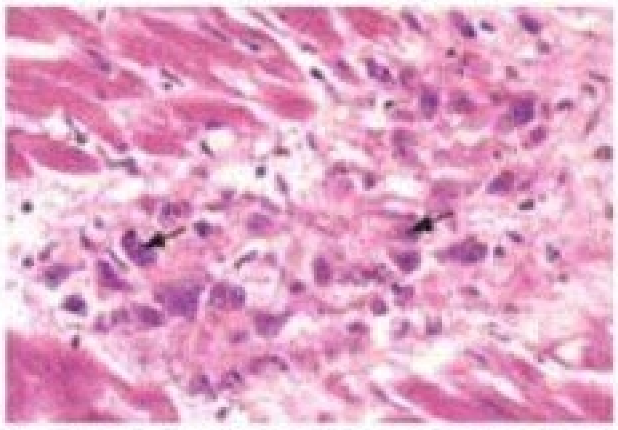
* Mitral valve stenosis

↓

Fish mouth/ button hole
deformity



ASCHOFF BODY (ACUTE RHEUMATIC CARDITIS)
Myocardium showing circumscribed nodule of mixed mononuclear inflammatory cells with associated necrosis; within the inflammation, large activated macrophages show prominent nucleoli, as well as chromatin condensed into long, wavy ribbons (caterpillar cells).



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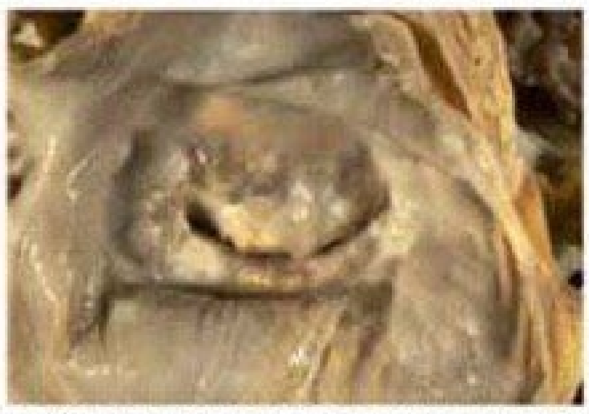


"FISH MOUTH" SHAPE MITRAL VALVE DUE TO CHRONIC RHEUMATIC SCARRING
Mitral valve seen from above in the left atrium.
The mitral valve demonstrates the typical "fish mouth" shape with chronic rheumatic scarring.

- Diagnosis : Revised Jone's Criteria
    - h/o Group A strept. inf + 2 major (or) (1major + 2minor)

MAJOR CRITERIA

1. Migratory poly arthritis :
    - MC involvement : Large joint
    - MC presentation
    - No residual deformality
2. Sydenham Chorea
    - involuntary rapid, purposeless movement
3. Erythema Marginatum
    - Geographical Red macular lesion in fase
4. Pan carditis
    - Fibrinous in nature
    - Bread & Butter carditis
5. Subcutaneous nodules

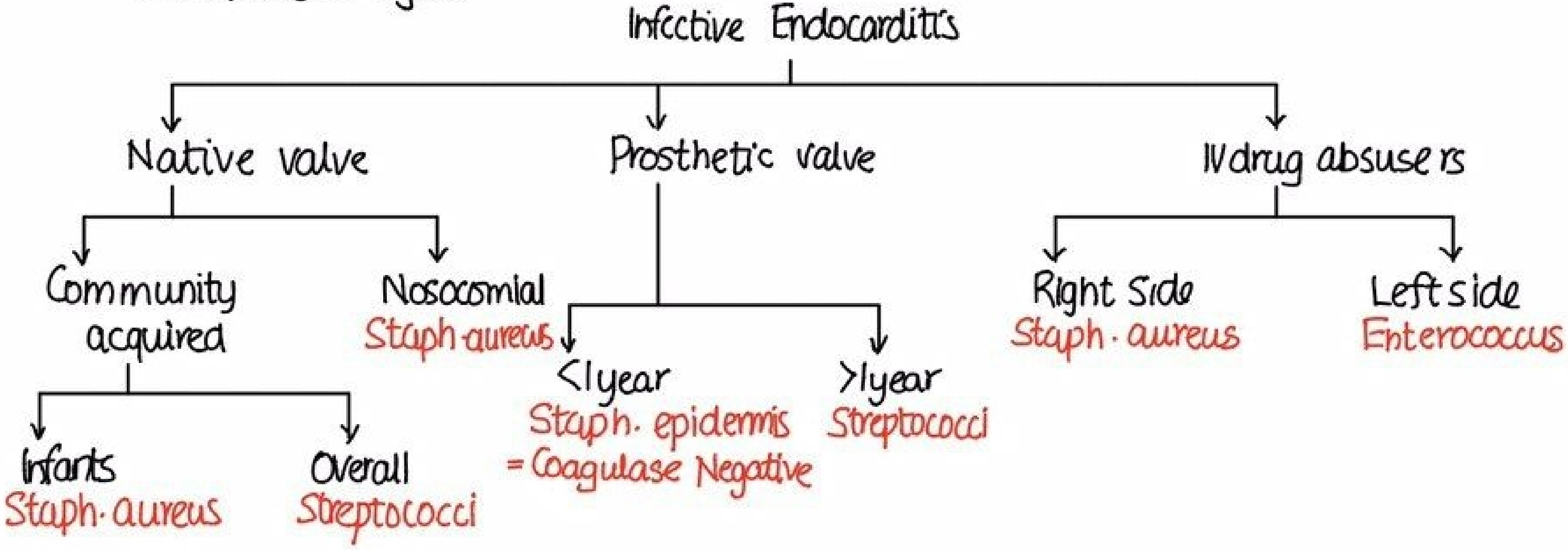
MINOR CRITERIA

1. Polyarthralgia
2. Fever (>38.5°C)
3. ↑ ESR
4. Prolonged PR interval on ECG

- MCC death in
    - Acute RHD : Endocarditis
    - Chronic RHD : Myocarditis
    - Overall : Myocarditis

INFECTIVE ENDOCARDITIS

- endocardial inflammation caused by infectious agent. causing myocardial & valvular damage
- MC infectious agent



- Diagnosis : Modified Duke's Criteria
  2 major + 0 minor (or) 1major + 3minor (or) 0Major + 5minor

MAJOR CRITERIA

1. Positive Blood culture for typical organism like
   - Streptococcus
   - Staphylococcus
   - HACKE group

   > 2 Blood culture positive ; 12hrs apart
2. On echocardiography
   Intra cardial mass/abscess/ valvular defect.
3. Single +ve Blood culture for Coxiella Burnetti

MINOR CRITERIA

1. Predisposing heart condition or IV drug abuse
2. Temperature >38°C
3. Immunological Phenomena
   - Osler Nodes Red maculopapular lesion/Immunocomplex deposits. Painful/tender s/c lesion. present in pulp of finger
   - Roth spots
     Oval retinal hemorrhages
     also seen in i) Leukemia
     ii) DM
     iii) Pernicious Anemia
4. Vascular phenomena :
   d/t septic emboli
   i) Mycotic aneurysms
   ii) Jane way lesion
   -Non tender red maculopapular lesions on palms & soles
5. Positive Blood culture
   not meeting major criteria

VEGETATIONS

Rheumatic Fever	Non Bacterial Thrombotic Endocarditis (Marantic Endocarditis)	Libman-Sack Endocarditis	Infective Endocarditis
* Small, firm & warty vegetation	* Small but friable ∴ more prone for embolisation	* medium sized verrucae or flat vegetation	* Large & irregular vegetations
* sterile	* sterile	* sterile	* Non-sterile
* present along the line of closure of valves	* present along the line of closure of valves	* present on both side of valve MC Site: Lower side (pocket of valves)	* present on both sides MC: Upper side
* non-destructive	* non-destructive	* valvular & myocardial damage	* Most destructive & Most prone for Embolisation
	* seen in hypercoagulable state Eg: AML-M3 ↑Estrogen cancers		

PERICARDITIS

A) Acute Pericarditis

d/t Viral inf. > Bact inf

↓

are of 4 types

(i) Fibrinous Pericarditis

- MC Type of Pericarditis
- Seen in :
  - post-MI
  - Uremia
  - Radiation

ii) Serous

- serous /watery secretion present
- Non-infective
- a/w A'I like RA
  SLE

iii) Hemorrhagic

- Blood present
- Seen in TB
  Malignancy
  Trauma

(iv) Caseous Pericarditis

- cheesy pericarditis
- seen in T.B

b) Chronic pericarditis

d/t TB

- pericardial fibrosis
  ⇒ whitish plaque on epicardium
  (Soldier's plaque / Milk spot)

MYOCARDITIS

- MCC of myocarditis : Herpes virus > Cox-sackie virus inf.
- most common helminth causing myocarditis : Trichinella spiralis

CARDIOMYOPATHIES

1. Dialated Cardiomyopathy

- dialatation of all 4 chambers of heart.

↓

diastolic compliance effected

↓

∴ These are Diastolic disorders

- Itiology : i) MC cause : Alcohol
  ii) Iron overload : $Fe^{3+} \rightarrow FR \rightarrow$ Myocyte hypertrophy
  ∴ Dialated CM > Restrictive CM in iron overload
  iii) Hereditary

  ↓ AD — Titin protein encoding gene mutation

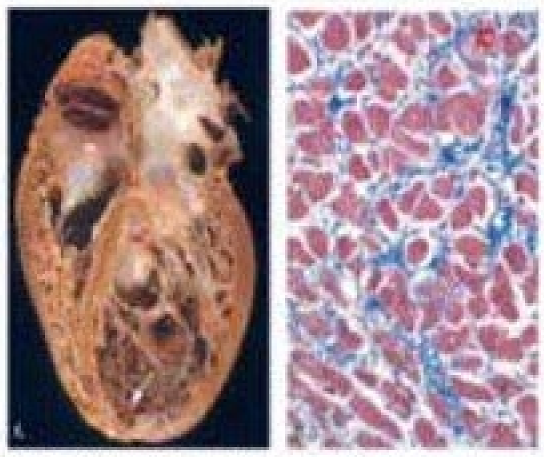
  ↓ XLR — Eg: Duchenne muscular dystrophy

- Morphology :

  Gross : Large, Flabby heart all chambers dialated
  cardiomegaly upto 900gm

  M/E : ∗ myocyte hypertrophy
  ∗ interstial fibrosis

for more notes join our telegram channel,"latest neet pg notes 2020" or join via link "t.me/latestpgnotes"



DILATED CARDIOMYOPATHY

A) Four-chamber dilatation and hypertrophy are evident. There is a mural thrombus (arrow) at the apex of the left ventricle(on the right in this apical four-chamber view). The coronary arteries were patent.

B) Histologic section demonstrating variable myocyte hypertrophy and interstitial fibrosis (collagen is highlighted as blue in this Masson trichrome stain).

-Variants of DCM

(1) Takotsubo cardiomyopathy
- aka Broken Heart syndrome
- occurs when patient is having extreme psychological stress

↓

↑ catecholamine

↓

act On Heart

↓

apical ballooning of LV apex
- compliance of heart compromise

↓

Myocardial stunning without any significant ECG changes
- M/E : showing contraction band Necrosis
- causes Sudden death

(2) Arrhythmogenic RV- CM
- It's an AD disorder
- a/w Gene mutations encoding protein Desmosomes
- Gross :

Thinning of RV wall d/t Fatty + Fibrous infiltaration
- M/E :

Normal myocardium replaced by fibrofatty infiltaration

↓

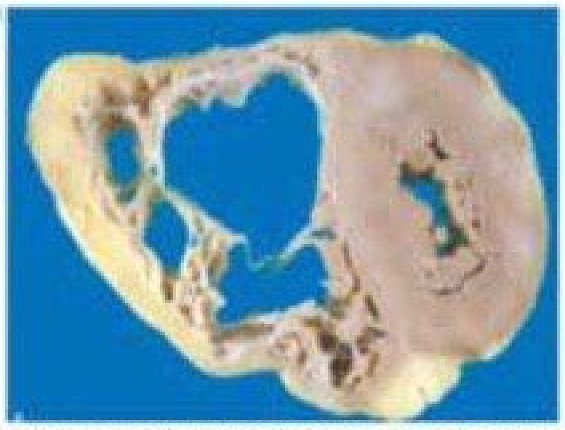
Thinning of myofibers
- sudden death d/t : ARRYHTHMIA

Arrhythmogenic RVCM may have a/w

i) Hyerkeratosis of palms & soles

ii) Wooly hair

These 3 together known as NAXO Syndrome d/t mutation in gene encoding Placoglobulin



ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Gross myocardium of the right ventricular free wall is partially replaced by fibro-fatty tissue (arrow) that typically begins in the epicardial region and at later stages expands transmurally.

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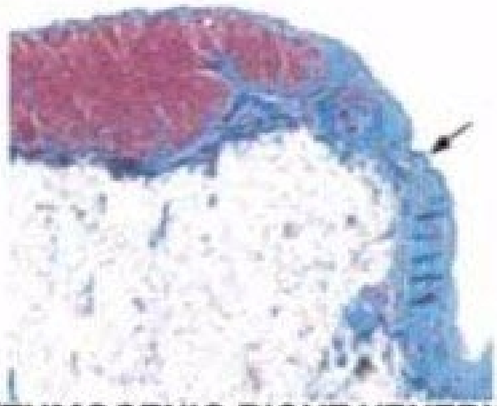
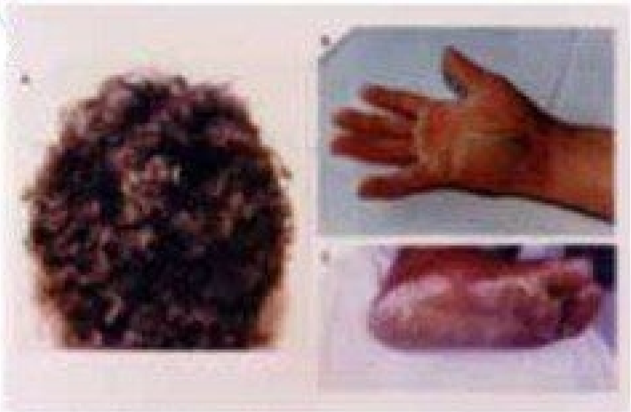


ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Endomyocardial biopsy demonstrating fatty (black arrow) replacement of the right ventricular myocardium. Strands of myocardium are still visible (white arrow).



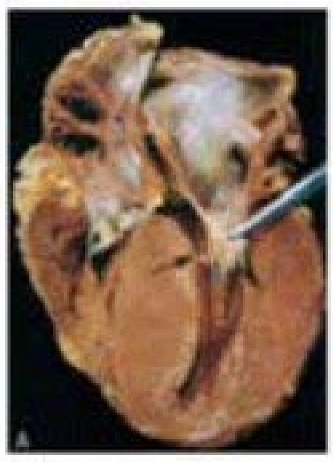
NAXOS SYNDROME

It is associated with mutations in the gene encoding the desmosome associated protein plakoglobin.

It is a disorder characterized by -

a) Arrhythmogenic right ventricular cardiomyopathy (image).

b) Wooly hairs and Hyperkeratosis of plantar and palmar skin surfaces (image).



HYPERTROPHIC CARDIOMYOPATHY

Showing massive asymmetric interventricular septal hypertrophy without ventricular dilatation leading to banana like configuration due to compression of left ventricular cavity by asymmetric bulging of septum.

2. Hypertrophic Cardiomyopath

- young athelete sudden death while playing /physical exertion
- Etiology : → mutation in gene encoding β-myosin heavy chain (β-MHC)
- Gross : (i) assymetrical interventricular septal hypertrophy

↓

involving Sub-aortic area

↓

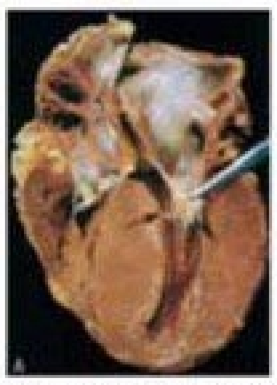
causes stenosis

∴ example diastolic disorder

↓

Sudden death

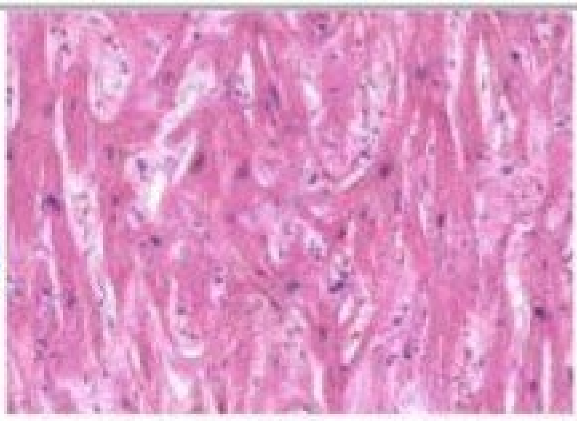
(ii) Banana shaped cavity (No dilatation, only hypertrophy)



HYPERTROPHIC CARDIOMYOPATHY

Showing massive asymmetric interventricular septal hypertrophy without ventricular dilatation leading to banana like configuration due to compression of left ventricular cavity by asymmetric bulging of septum.

- M/E : (i) Myocyte disarray : diagnostic
  aka Angulated Myofibers
  Helter-skelter type of disarray



HYPERTROPHIC CARDIOMYOPATHY (MICROSCOPY)

Showing myocyte disarray where myocytes are oriented at bizarre and variable angles to each other (pathognomonic feature).

3 Restrictive Cardiomyopathy

- diastolic dysfunction → Defect in Ventricular filling
- d/t i) Iron overload
  ii) amyloidosis
- ventricles will be normal
  atrium is dialated
  interstitial fibrosis on section of Heart

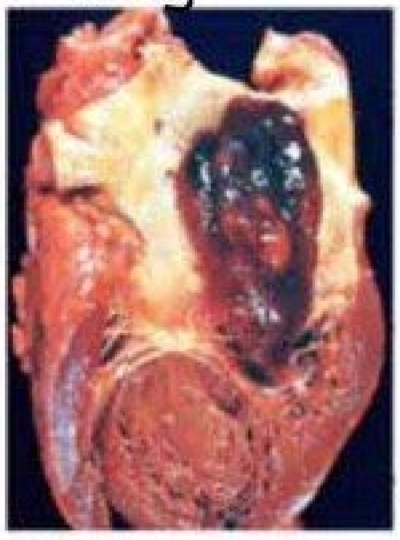
CARDIAC TUMOR

- MC cardiac tumor : Metastases i.e Secondaries
  MC metastases : Bronchogenic / Lung cancer
  MC site of metastatic deposit : Pericardium
- Cardiatric tumor

Pediatric age	Adult age group
• MC Benign tumor : Rhabdomyoma	• MC Benign tumor : Myxoma
• MC 1° Malignancy : Rhabdomyosarcoma	• MC 1° malignancy of heart : Angiosarcoma

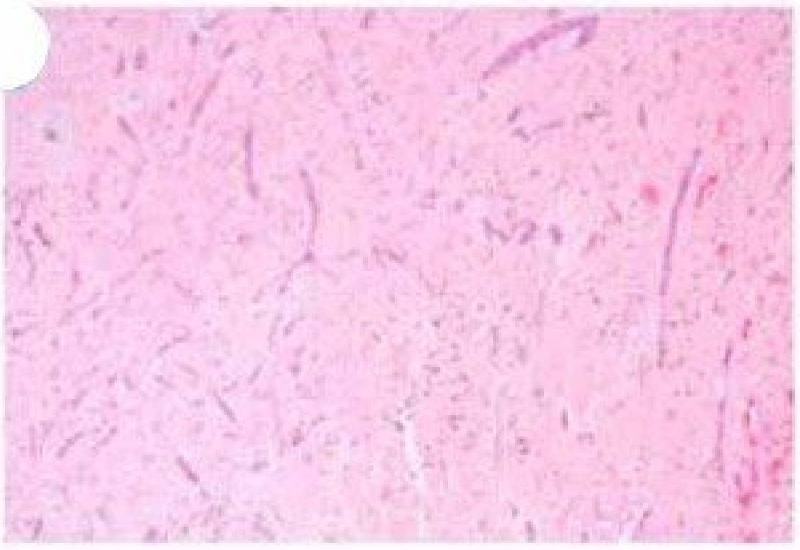
CARDIAC MYXOMA

- F > M ; 40-60 yrs
- sporadic > familial
  ↳ a/w : AD condition called as Carney's Syndrome.
  consist of i) MYXOMA
  ii) Pigmented Skin Lesion
  iii) Endocrine hyperactivity
- Gross : • MC Site Left atrium : Fossa ovalis
  • Tumor plop sound on auscultation
- M/E : • Mucopolysaccharide
  • Stellate mesenchymal Tumor cells
  called as Lepidic cells



ATRIAL MYXOMA

A large pedunculated lesion arises from the region of the fossa ovalis and extends into the mitral valve orifice.



CARDIAC MYXOMA

Showing typical stellate or spindle cells (Lepidic cells) in abundant myxoid matrix along with hemosiderin laden macrophages

LUNGS

CONGENITAL ANOMALIES

1. BRONCHO PULMONARY SEQUESTRATION

↓ discrete/seperate mass

- seperate mass of lung tissue with no connection to Ⓝ airway system
- Blood supply from Aorta
- It's of 2 types

Intralobar
seperated lung tissue is within lung parenchyma

Extralobar
seperated tissue is outside Ⓝ Lung parenchyma

- These are predisposing to risk for
  i. Infections
  ii. Bronchiectasis (MC Intralobular)

3. ATELETASIS

- can be of Hereditary or acquired
- Atelectasis means collapse of Lung
  defined as incomplete expansion of Lung in infants
  or
  collapse of already inflated Lung
- Acquired Atelectasis are of

Resorption
- ✱ reversible
- ✱ d/t absorption of O_2 into dependentant part of alveoli
  This is d/t ↑ mucus secretion into bronchi
  (or) foreign body aspiration
  (or) Bronchial Neoplasm
- ✱ Mediastinum shift towards atelectasis

Compression
- ✱ reversible
- ✱ d/t ↑ pleural fluid within pleura
  Reasons
  (i) Pleural Effussion (Tumor, TB, CHF)
  (ii) Tumor
  (iii) Pneumothorax
- ✱ Mediastinum shift away from atelectasis

Contraction
- ✱ Irreversible
- ✱ d/t Fibrotic lesion of Lung tissue

- Clinical significance : ↓ oxygenation ⟶ ↑ risk of infections.

3. ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

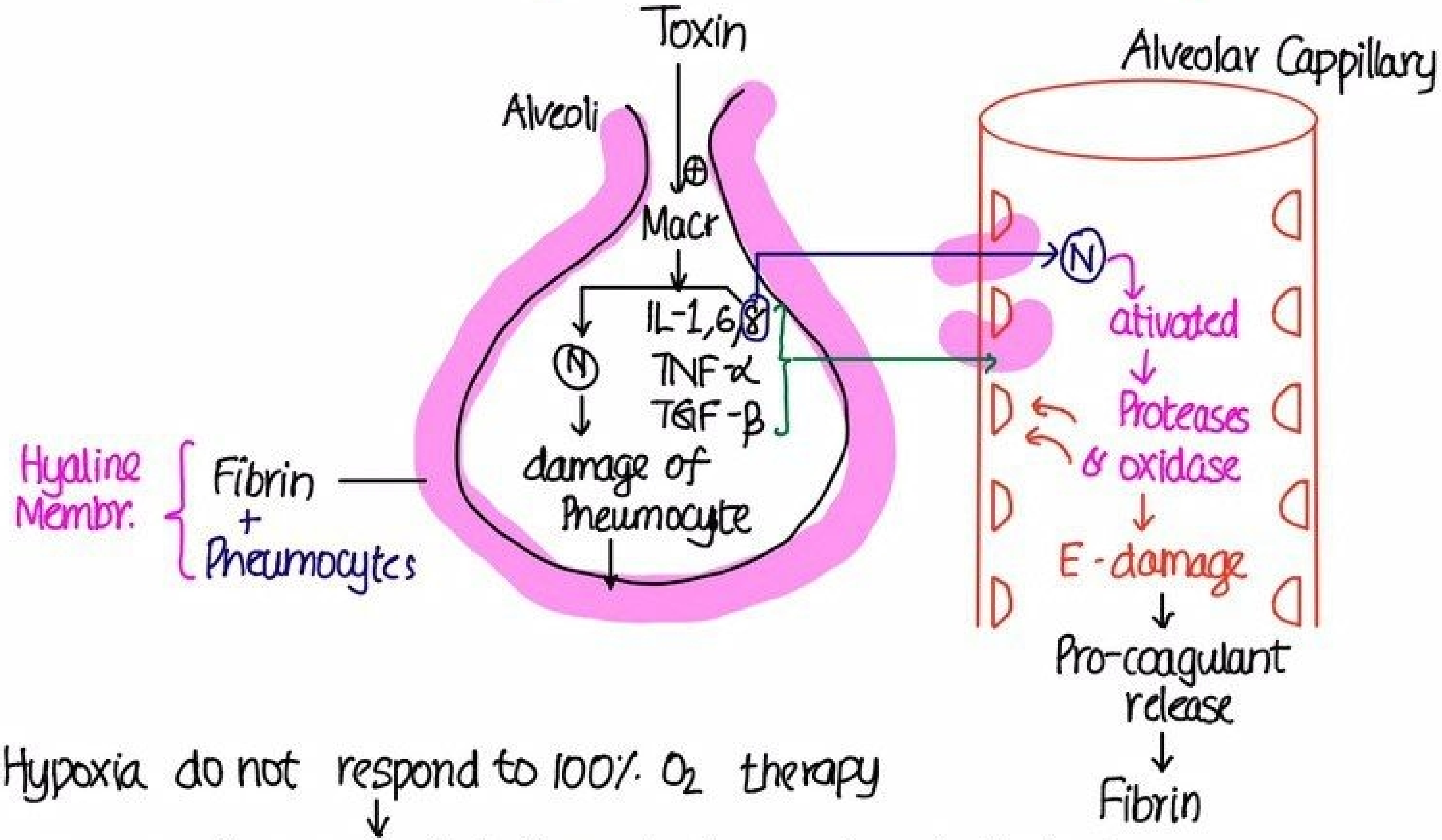
- aka Hyaline Membrane disease
  Diffuse alveolar damage
- Hypoxia , Bilateral pulmonary infiltarates without any cardiac abnormality : Non Cardiogenic pulmonary Edema

↓
ARDS

- Etiology : Acute Lung injury

  ↓ mild
  ↓ Severe → ARDS

  Etiology of acute Lung injury
  - i) Unknown (idiopathic) → Acute Interstial Pneumonia i.e ARDS with Unknown Etiology
  - ii) Toxins
  - iii) Infections
  - iv) Trauma
  - v) Cardiopulmonary Ressucitation
  - vi) Uremia
- Pathogenesis : d/t damage of endothelial cell > Pneumocytes (M. Important)

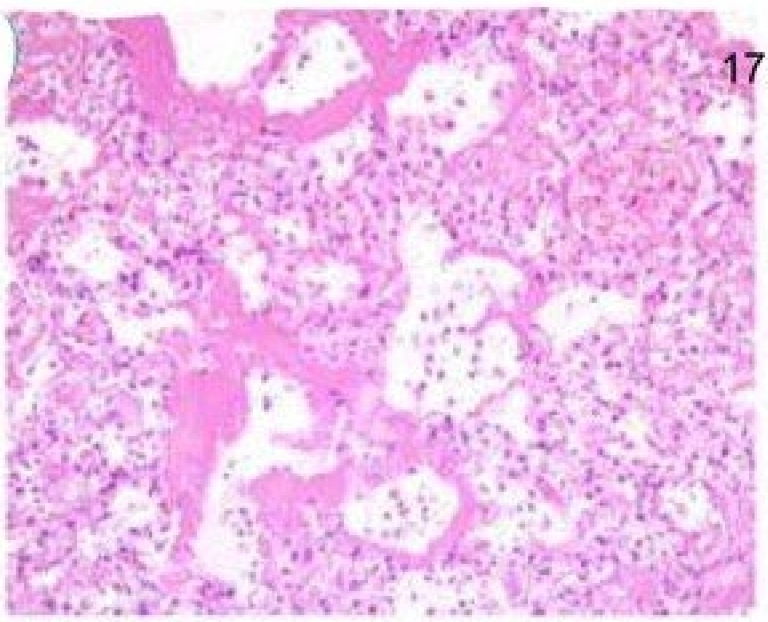


- Hypoxia do not respond to 100% O_2 therapy

  ↓
  as a small amount leak through damaged endothelium
  ↓
  None of O_2 can undergo gaseous exchange d/t Hyaline membrane
  ↓
  Persistent hypoxemia
  ∴ aka Shock Lung.

- Gross : Edematous & Wet Lung tissue

- M/E :
  - i· Neutrophilic infiltarate
  - ii. All alveoli are covered by hyaline membrane
    ↓
    ∴ diffuse alveolar damage
  - iii. Fibrinous exudates
- C/f : • Earliest : Dyspnea & Tachypnea
  ↓
  Hypoxia & Cyanosis
  - • Chest X-Ray : B/L pulmonary infiltarate
- T/t : • treat underlying cause
  - • severe case = Mechanical ventillation
- 40% mortality rate (Poorer prognosis)



DIFFUSE ALVEOLAR DAMAGE (ACUTE RESPIRATORY DISTRESS SYNDROME).
Lungs alveoli are collapsed, and many others are distended and lined by pink fibrinous hyaline membranes.

OBSTRUCTIVE	RESTRICTIVE
* ↑ resistence to air flow	* ↓ expansion of lung parenchyma ↓ ↓ Total Lung capacity
* Eg : Obstructive Pulmonary Disease (OPD) ↓ Bronchial Asthma Bronchiectasis Chronic Bronchitis } Chronic Emphysema } OPD	* Eg Obesity Neuromuscular disorders Interstilial Lung pathology

OBSTRUCTIVE PULMONARY DISEASE

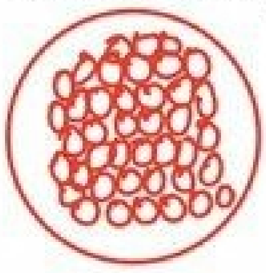
1. BRONCHIAL ASTHMA

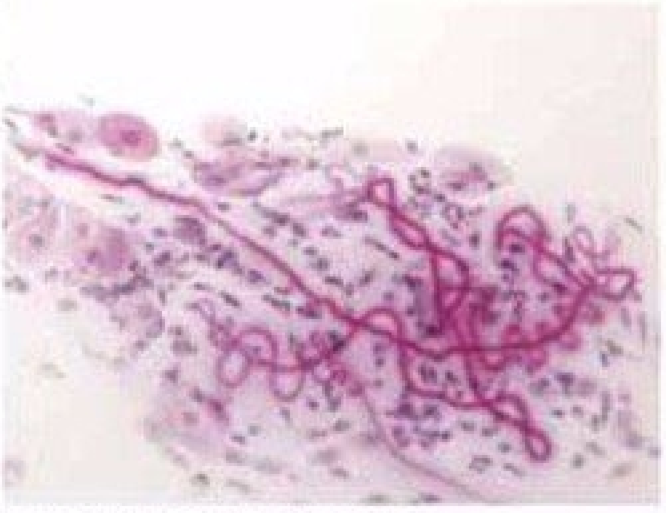
- They differ from other OPD by Reversible Bronchospasm
- It's a chronic relapsing inflammatory disorders.
  ↓
  smooth muscle hyperactivity & hypersecretion of mucus
  ↓
  Bronchospasm (Reversible)
- Etiology : • Atopy (a/w Chromosome 5q)
  - • Genetics :
    - i. Strongest & most consistent association : IL-13 gene polymorphism
    - ii. a/w ADAM-33 gene polymorphism
      ↓
      Responsible for : i. Smooth muscle hyperplasia
      ii. fibroblastic proliferation
- Morphology :
  - Gross : • Mucus plug within bronchi
  - M/E : Sputum cytology (3 bodies) i· Curschman - spiralis : Mucus plug with Tracheal Ring shadow

ii. **Charcot Leyden Crystals** : Eosinophilic granular protein made up of Galectin-10

Eosinophilic needle like crystal

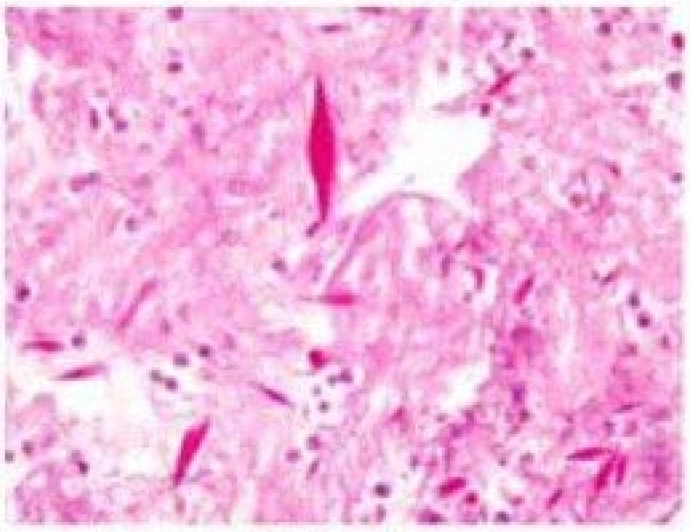
iii. **Creola Body** : Cluster of epithelial cells within mucus plug





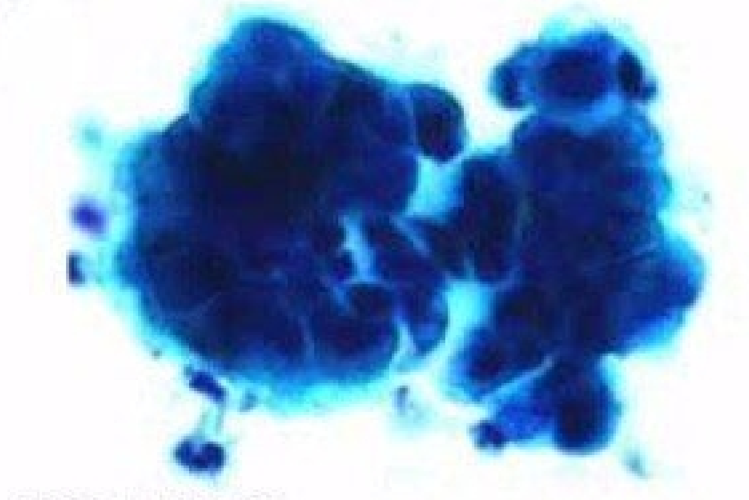
CURSCHMANN'S SPIRALS

These are a microscopic finding in the sputum of asthmatics consisting of spiral-shaped mucus plugs from subepithelial mucous gland ducts or bronchioles.



CHARCOT-LEYDEN CRYSTALS

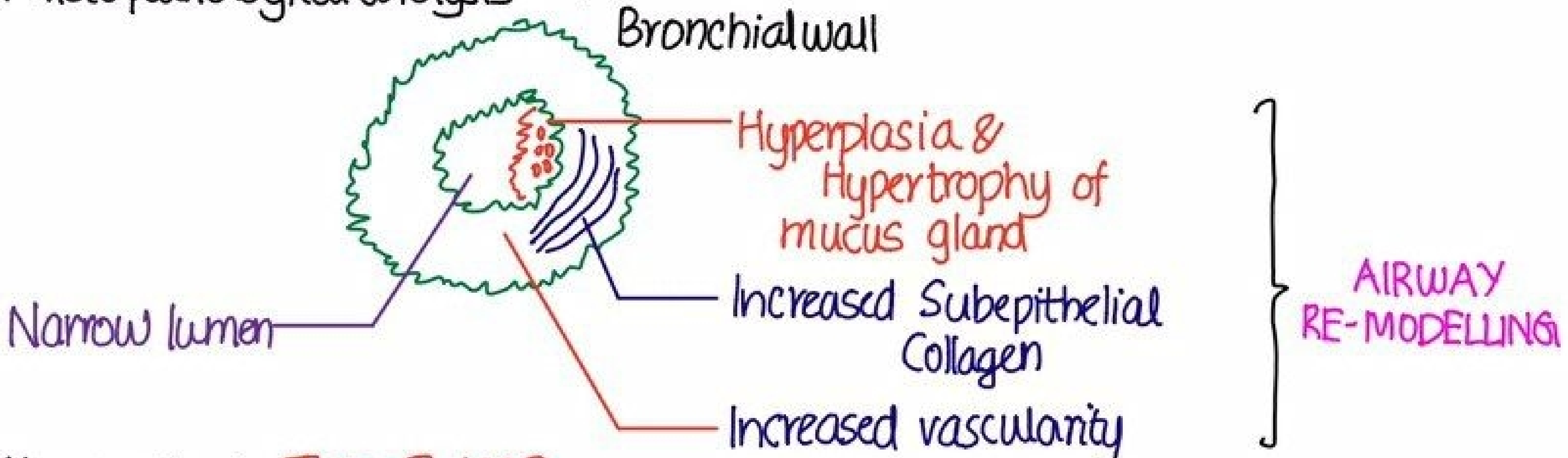
Needle like eosinophilic crystal made-up of eosinophilic protein called galectin-10.



CREOLA BODY

Creola bodies are clusters of ciliated columnar cells sloughed from the bronchial mucosa of a patient with asthma.

- On histopathological analysis :



Bronchial wall
Hyperplasia & Hypertrophy of mucus gland
Increased Subepithelial Collagen
Increased vascularity
Narrow lumen
AIRWAY RE-MODELLING

- Pathogenesis : Type-I HSR
- C/f : i. Wheezing iii. Cough
  ii. Chest tightness iv. Dyspnea

BRONCHIAL ASTHMA

↓ ATOPIC

- pediatrics
- ⊕ family history of allerg
- ↑ IgE in serum

Eg: i. Allergic Bronchial asthma
ii. Allergic Bronchopulmonary Aspergilloma
iii. Occupational Asthma

↓ NON-ATOPIC

- Adults
- No family history
- Ⓝ Sr IgE

Eg : i. Cold indused Bronchial Asthma
ii. Exerscise induced Bronchial Asthma
iii. Drug (MC : Aspirin)

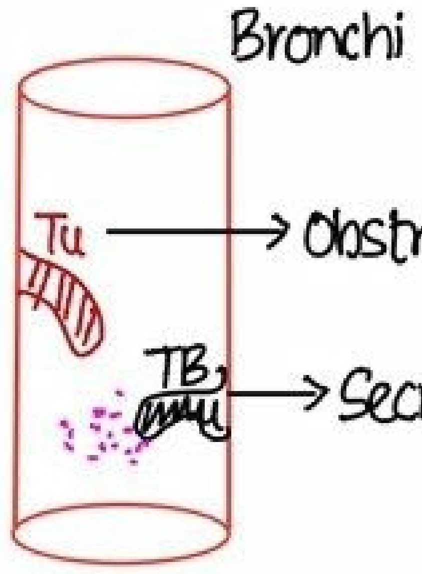
2. BRONCHIECTASIS

- Permenent Abnormal dialatation of dialatation d/t Necrotising & destructive inflammation of bronchi & bronchioles
- Etiology :
  - i. Infections (Eg: TB)
  - ii. Obstruction d/t Tumor mass
  - iii. Congenital disorders
    - a) Cystic Fibrosis
    - b) Primary Ciliary dyskinesia syndrome
      - AR
      - d/t mutation in Dynein protein mutation ↓ Cilliary motor movement
      - >50% cases a/w Kartagener - Syndrome
        - i. Recurrent infection (Eg: Sinusitis)
        - ii. Bronchiectasis
        - iii. Situs inversus (Eg: Dextrocardia
        - iv. Infertility

Females
as Oviductal cillia is required for ovum implantation within Fallopian tube

Male
↓ sperm motility (Asthenozoospermia) d/t Cilliar pro. defect

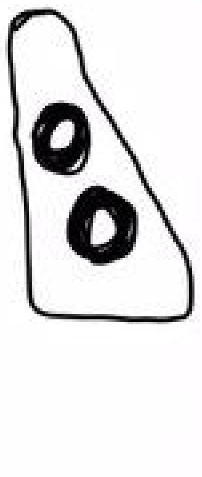
- Pathogenesis :

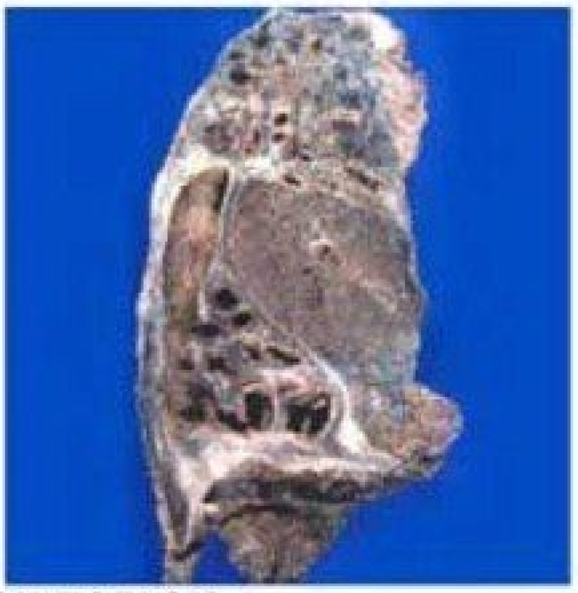


Tu → Obstruction → Infection → Necrotising Inflammation

TB → Secretion → Obstruction → Necrotising Inflammation

- Gross : Cut section
  - i. Dialated Bronchi
  - ii. Thickening of bronchial wall





BRONCHIECTASIS
a slice of lung showing markedly dilated bronchi, with thickening of the bronchial walls and collapse and fibrosis of the pulmonary parenchyma

- C/f :
  - Persistent Fever, Cough with purulent sputum
  - Cough : morning rise ⊕ positional change
- Complication :
  - i. Lung abscess
  - ii. Renal abscess
  - iii. Suppurative Arthritis
  - iv. AA Amyloidosis

Not a pre malignant lesion

3. CHRONIC BRONCHITIS

- aka Blue Bloaters
- Persistent productive cough for >3months for >2 consecutive years. without any non-identifiable causes.
- Etiology : Smoking (CB is strongly a/w)
- Pathogenesis : Chronic irritation of Bronchi
- M/E : i. earliest finding Mucus gland hypertrophy + Mucus hypersecretion
  ii. Goblet cell metaplasia
  iii. Inflammation → fibrosis ; Bronchiolitis

# Risk of Lung cancer

⊛ Reid's index = ratio of thickness of $$\frac{\text{Mucus gland Hypertrophy}}{\text{Bronchial wall thickness b/w Epithelium \& Cartilage}}$$

Normal Ratio = <0.4
In C.B = >0.4

- C/f : Hypoxia, Cyanosis, Cough, Fever
  ⊛ Hypercapnea ⟶ ∴ Bluish colour ∴ aka Blue Bloaters

4. EMPHYSEMA

- Irreversible dialatation & destruction of acini & their elastic tissue.
- Respiratory tree

Trachea
↓
Bronchi
↓
Bronchioles
↓
Terminal Bronchiole
↓
Respiratory Bronchiole
↓
Alveolar duct
↓
Alveoli

ACINUS : distal to the Terminal Bronchiole → Site of emphysema.

- Pathogenesis : Imbalance b/w Proteases & Anti-Proteases

Proteases ↓ Eg : Elastase ↓ Source : Macrophages, Neutrophil.

Anti-Proteases ↓ Eg : α_1-Anti trypsin

- Types of Emphysema

CENTRIACINAR

MC Clinically
MC histologically
MC Overall

- a/w
  - i. Cigarette Smoking
  - ii. Coal worker
- Pathogenesis:

Smoking $\xrightarrow{+}$ Macrophage
↓
Proteases
(Matrix-Metallo Protease)
- Resistant to α_1-AT
- digest α_1-AT

↓
Elastin damage
↓
Emphysema

- Gross:
  - i. Alveolarduct & alveoli spared
  - ii. Only Resp. Bronchioles affected

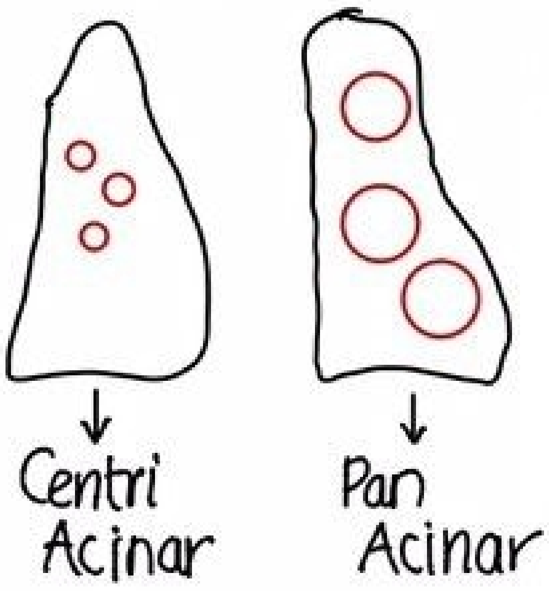
↓
Small Cavity, Thick Ⓝ wall

PANACINAR

- a/w Congenital def. of α_1-AT
- Pathogenesis:

Neutrophilic protease
↓
damage of elastic tissue

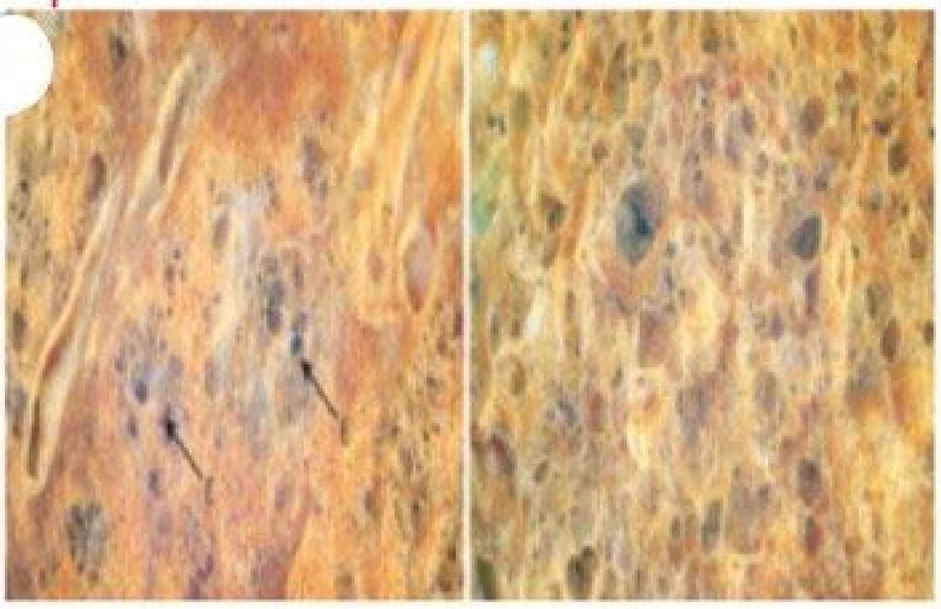
- Gross:
  - All Resp. Bronchiole + Alveolar duct + Alveoli effect
- Lung cut section
  - Bigger cavity
  - Thin wall



DISTAL

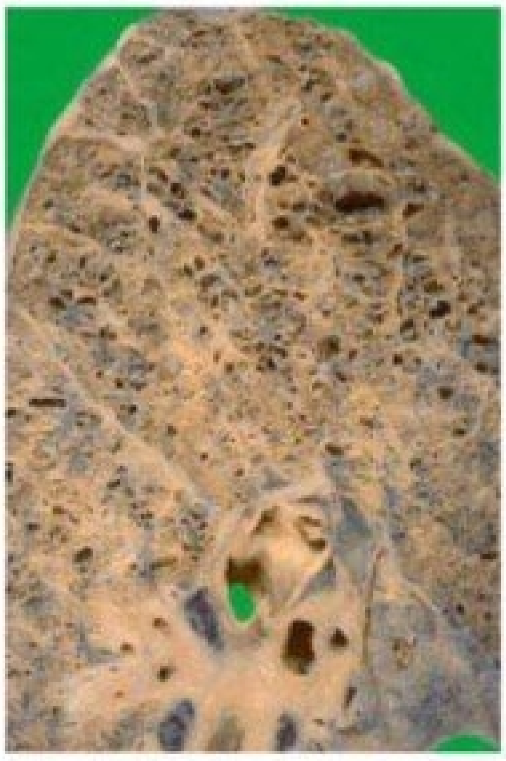
- a/w Spontaneous pneumothorax

IRREGULAR



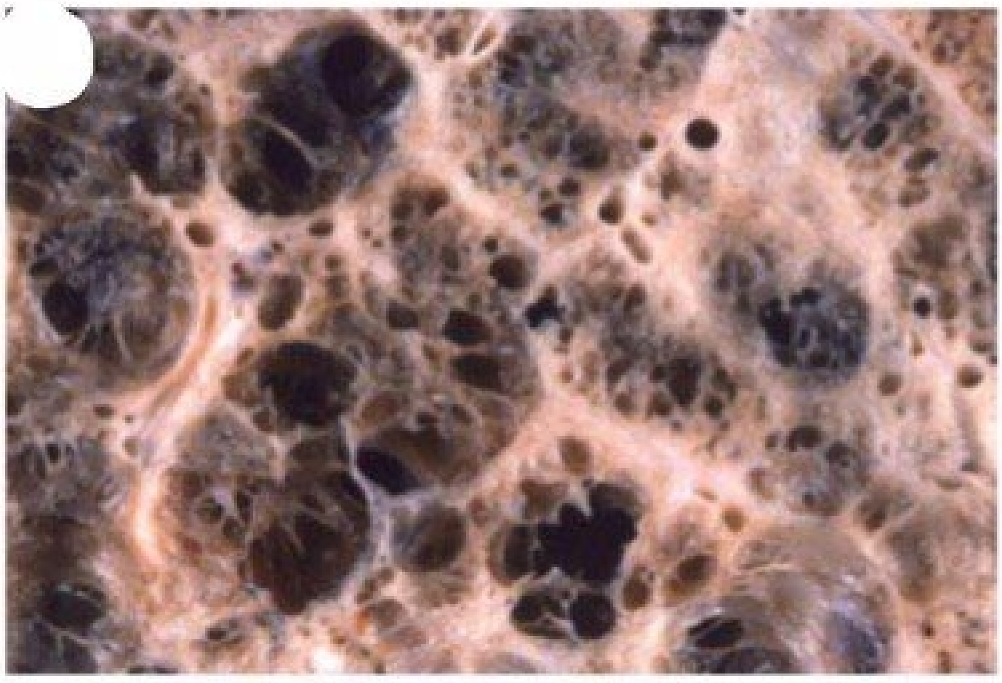
EMPHYSEMA

Centriacinar emphysema: lung shows expanded airspaces around respiratory bronchioles.
Panacinar emphysema: upper lobe of lung showing more diffuse enlargement of airspaces.



CENTRIACINAR EMPHYSEMA

lung shows expanded airspaces around respiratory bronchioles.



PANACINAR EMPHYSEMA

upper lobe of lung showing more diffuse enlargement of airspaces.

- Clinical features
  - i. Cough
  - ii. Dyspnea
  - iii. Wheezing
  - iv. Barrel shaped chest
  - v. Prolong expiration

} Symptom appear loss of >1/3rd of parenchyma

↓
Over ventilation
↓
Hyper oxygenation
↓
looks Pink colour ∴ aka Pink puffers

RESTRICTIVE LUNG DISEASE

INTERSTIAL FIBROTIC LUNG DISORDER

- aka Interstitial Lung disorders

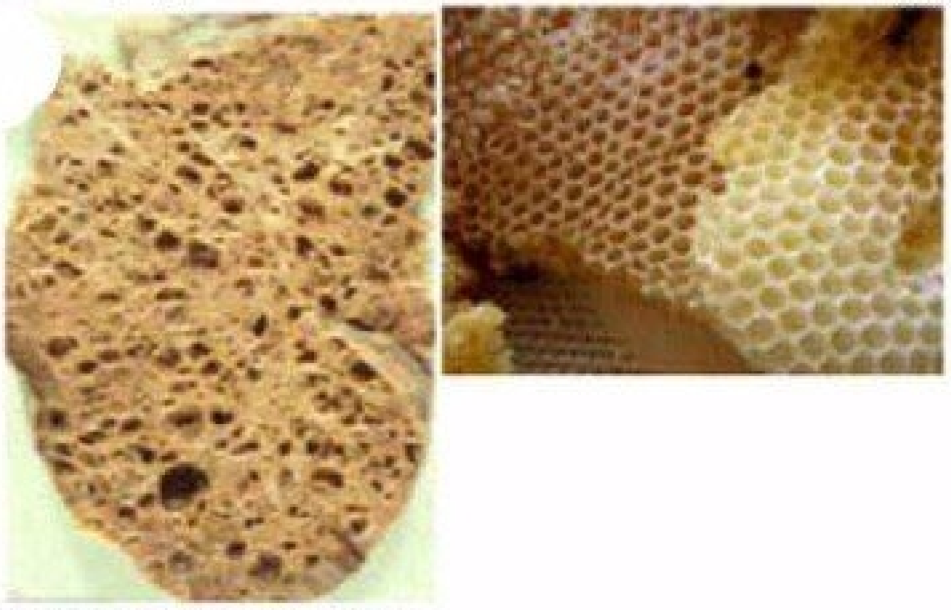
- collection of Lung pathology where inflammation

↓ induces

Fibrosis of Lungs

↓

Terminal Event : HONEYCOMB LUNG



HONEYCOMB LUNG
This can be the end-result of a number of fibrosing lung diseases, including usual interstitial pneumonia.

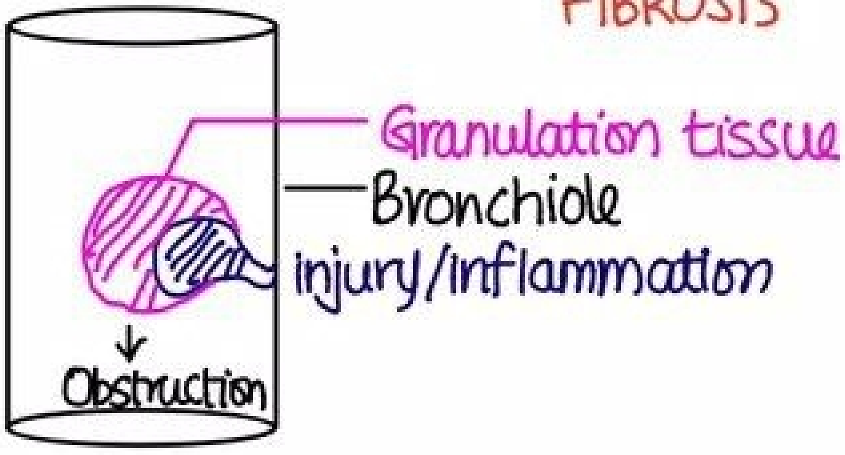
- It consist of

1. CRYPTOGENIC ORGANISING PNEUMONIA

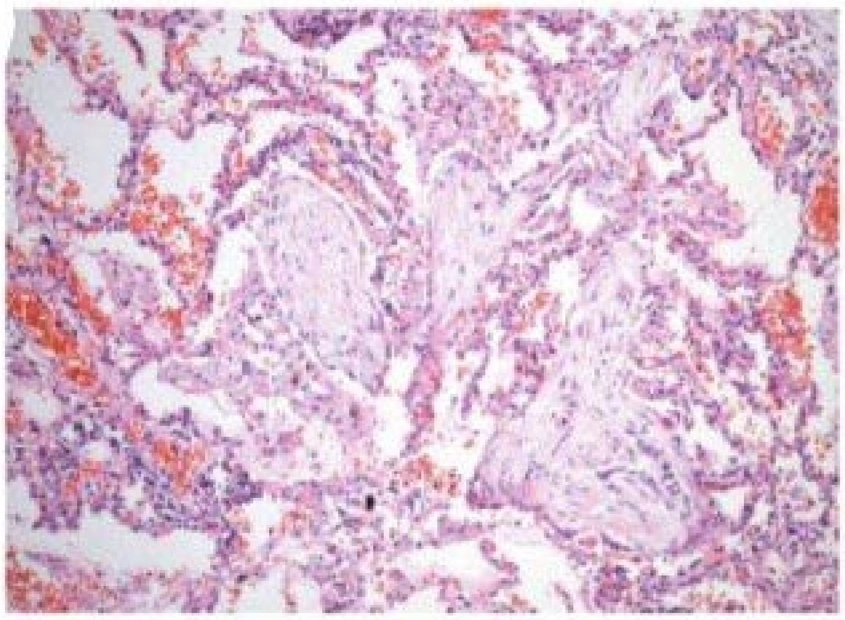
- Older name : Brochiolitis Obliterans
  Organising Pneumonia (BOOP)
- Etiology : idiopathic
- Pathology : Inflammation of interstium

↓

Release Cytokine
TGF-β
↓
FIBROSIS



Inflammation / injury
↓
Granulation tissue
(Polypoidal growth)
↓
Obstruction of Bronchioles



CRYPTOGENIC ORGANIZING PNEUMONIA
with intra-alveolar spaces filled with of fibromyxoid granulation tissue (Masson bodies).

- Microscopic Examination :
  i. Collagenous granulation tissue
  Inside the alveoli
  called as Masson Body
  ii. Inflammatory cells
- No honey comb formation

2. PNEUMOCONIOSIS

- group of non neoplastic lung pathology caused by inhalation of aerosol

↓

Eg: Silica, Coal, Asbetos (Organic/Inorganic)

- Risk factors : ① Size of particle
  Dangerous particle size : 1-5 μm
  (macrophage can't phagocytose particle size < 5μm)
  ② Solubility
  More soluble , more toxic
- Pneumoconiosis consist of
  i. Coal worke Pneumoconiosis } involve upper
  ii. Silikosis (Most prevelent occupational disorders) } lobe
  iii. Asbetosis } involve lower lobe

- Pathogenesis : Particles (<5μm)

↓

Reach to alveoli (macrophage) ⟶ Not able to phagocytose

↓ ⊕

inflammation

↓

Fibrosis & Scarring ⟵ Release of TGF-B

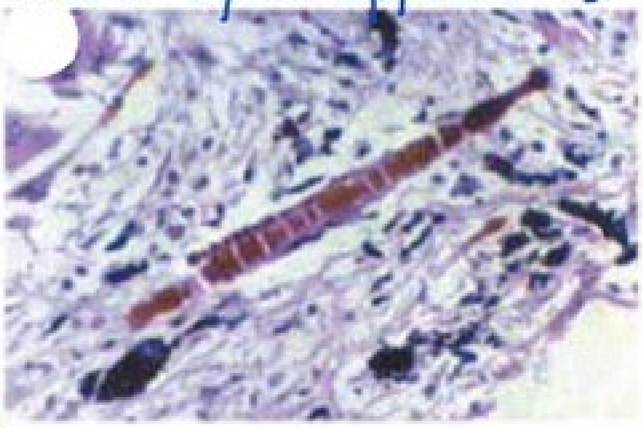
- Disorder will progress even after end of exposure
- Presence of Ferruginous Bodies

↓ consist of

Fe + Glycoproteins + organic & inorganic dust fibers

It's a/w all types of Pneumoconiosis

MC a/w Ashetosis (Show beaded / dumbel shaped appearance)



ASBESTOS BODY

Scarred lung tissue showing golden brown and beaded ferruginous bodies.

1. COAL WORKER PNEUMOCONIASIS

- d/t ingestion coal particles
- aka Antracosis
- Clinical stages

i) Asymptomatic

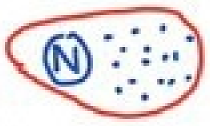
* nosymptoms

ii) Simple CWP

* coal-macules are seen

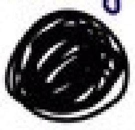
↓

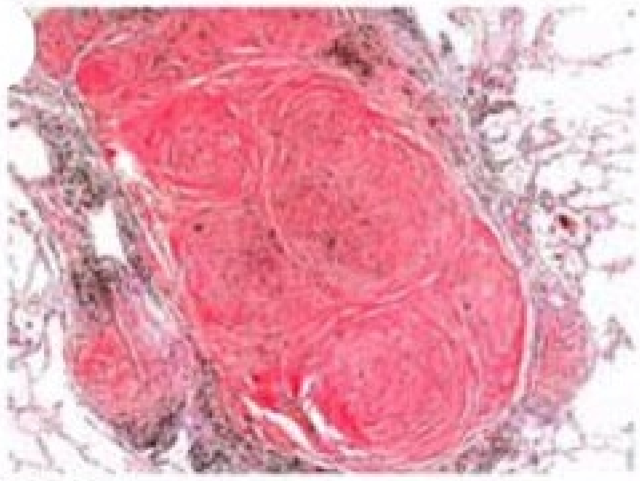
Macrophage laden with coal particle



iii) Progressive Massive Fibrosis

* forms Large Black Collagenous Scar





SILICOSIS

A silicotic nodule is composed of whorled, hyalinized, fibrous nodules of collagen. Actively proliferating edge is composed of pigmented macrophages.

2. SILICOSIS

- Most prevelent occupational disease
- aka Grinder's disease
- Silica → Crystaline, Amorphous

Crystaline ↓ More pathogenic

Silica ↓ inhibit T_{H1} ⟶ ↓ cell mediated immunity ⟶ ↑ risk of TB (Silico tuberculosis)

- Silica mixed with other substances ⟹ Less pathogenic
- M/E : Large silica layden collagenous modules

# on polarised microscopy : Birefringerent silica seen.

3. ASBETOSIS

- 2 types of pathogenic fibers

Serpentine fibers
Eg: Chrysolite

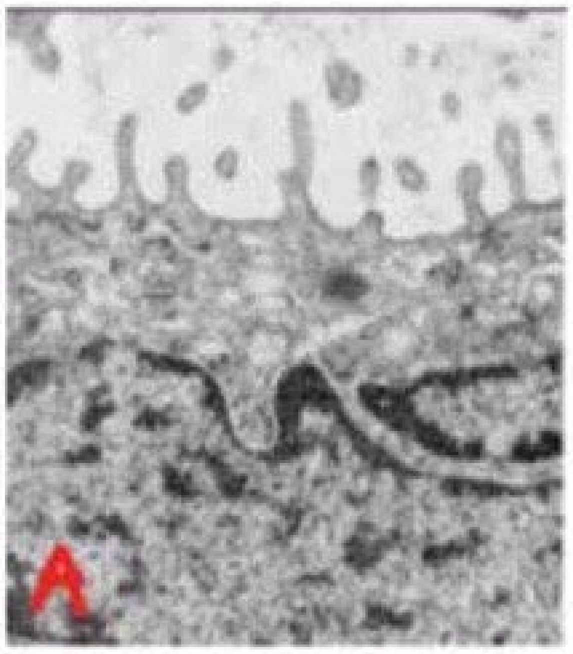
Straight fibers (Most pathogenic)
Eg: Amphibole
Amosile
Crocidolite
↓
MC a/w Carcinoma

- Exposure of Asbetosis $\xrightarrow[\text{after 5-10yrs}]{}$ Asbetosis
- Most common finding : • Diffuse calcific pleural plaque
  MC Site : Parietal Pleura
  (Antero posterior parietal pleura)
- Other findings : • Diffuse interstial lung Fibrosis

# cancer a/w Asbetosis :

MC Cancer
Bronchogenic Cancer
(I.P = 15-20yrs)
Squamous Cell ca << Adeno Carcinoma
↓
Glandular pattern
↓ seen in both

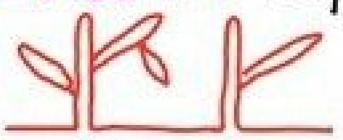
Most specific
Mesothelioma
(I.P=35-40yrs)



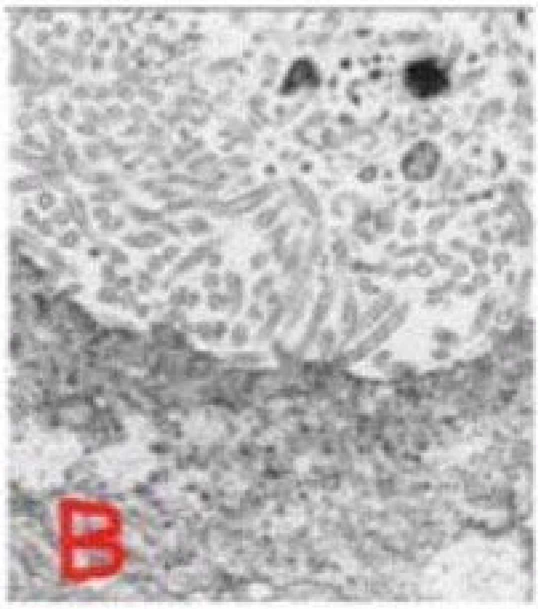
ADENOCARCINOMA
On electron microscopy they will show Short non-branching microvilli.

Adenocarcinoma
↓
IHC: TTF-1
Napsin-A
↓
On EM:

small non branching microvilli

Mesothelioma
↓
IHC : • CK-5/6
• Calretinin superior to CK-5/6
↓
On EM:

Large Branching microvilli

# Smoking is having addictive Risk factor for Bronchogenic Ca
No risk in mesothelioma.



MESOTHELIOMA
Electron microscopy will show long slender microvilli with branching.

GRANULOMATOUS INFLAMMATION

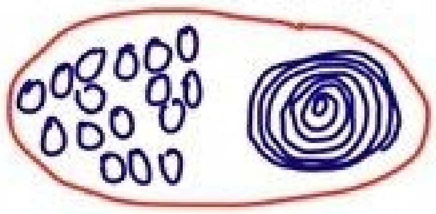
1. SARCOIDOSIS

- immunologically mediated disorder
- F>M
- Unknown Etiology
- Stronger association with HLA-A1, HLA-B8

- Pathogenesis : $Ag \xrightarrow{\oplus} CD_4 T_{H1} \longrightarrow IFN\text{-}\gamma \longrightarrow$ Granuloma formation

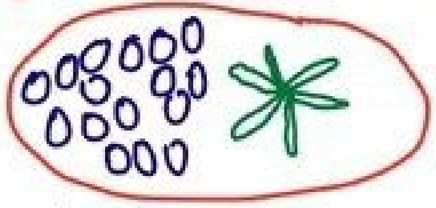
- M/E : • Lung/LN Biopsy : Non caseating granuloma
(=Naked granuloma)
Lymphocyte collar absent or scanty

• Giant cells with basophilic calcified laminated proteinaceous material called as Schauman Bodies



Foreign body Giant cell with Schauman Bodies

• Giant cells with stellate appearance of lipid bilayer - called as Asteroid Bodies



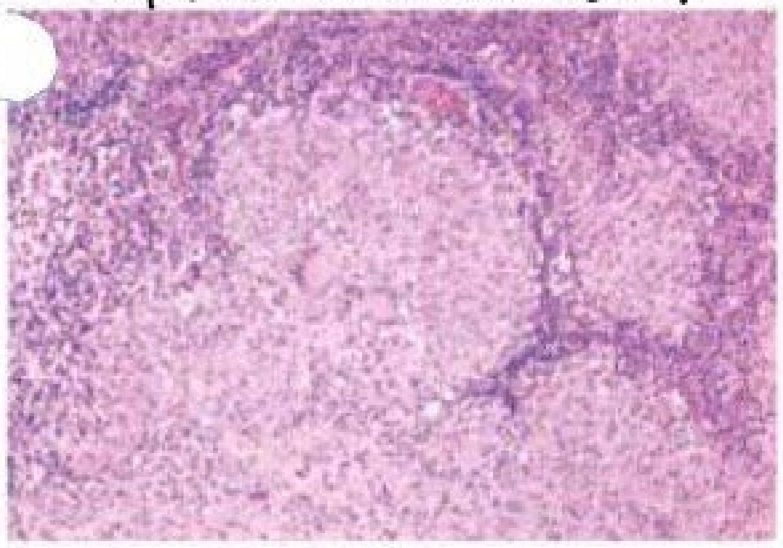
Asteroid Body

- Clinical Features :
  - Fever, Cough, Weight loss
  - predominently resp. difficulty
  - MC effected organ : Lung
  - MC LN effected : Bilater hilar LN enlargement
  - Mickulicz Syndrome : Lacrimal & Salivary Gland Enlargement
  - MC Hematological finding : Lymphocytopenia
  - MC Opthalmic finding : Anterior uveitis
  - a/w

Lofgren Syndrome
* consist of
i) Erythema Nodosum
ii) LN Enlargement (Hilar)
iii) Arthralgia
* a/w Acute Sarcoidosis

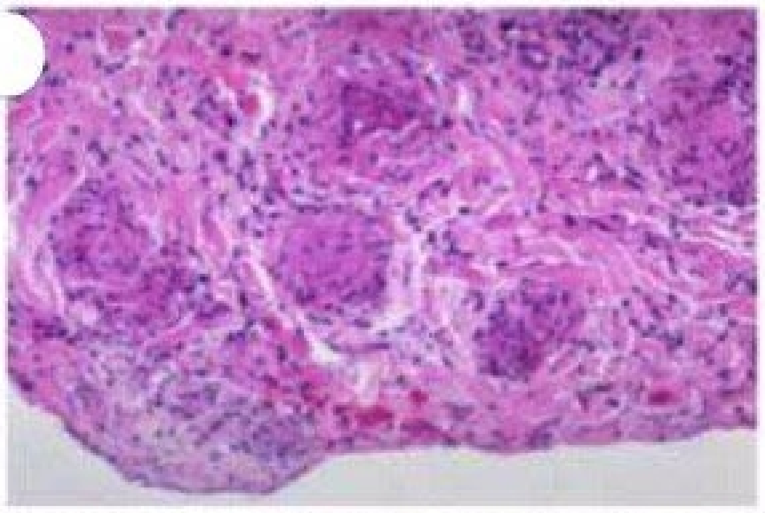
Heerfordt Waldenstrom Syndrome
* aka Uveoparotitis
* consist of
• Ant uveitis
• Parotitis
• Facial Nerve Palsy

- Diagnosis : Biopsy Non diagnostic
Diagnosis is by exclusion.

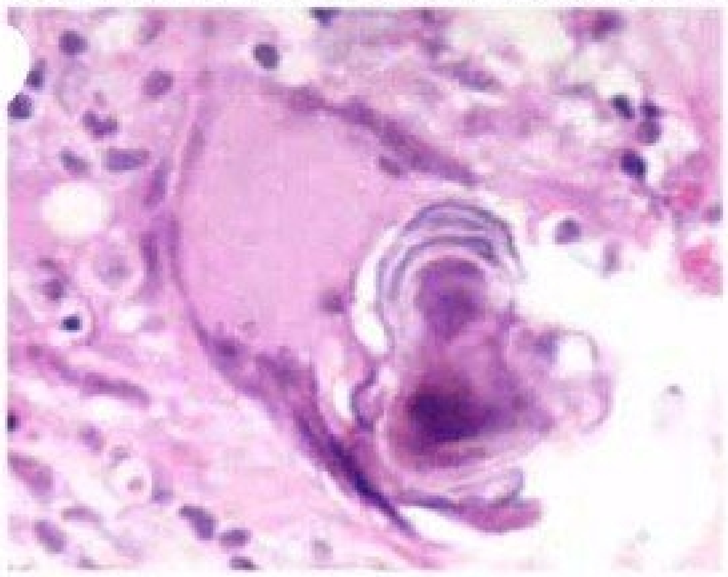


SARCOIDOSIS

microscopic view of non-caseating granulomatous inflammation, including giant cells.

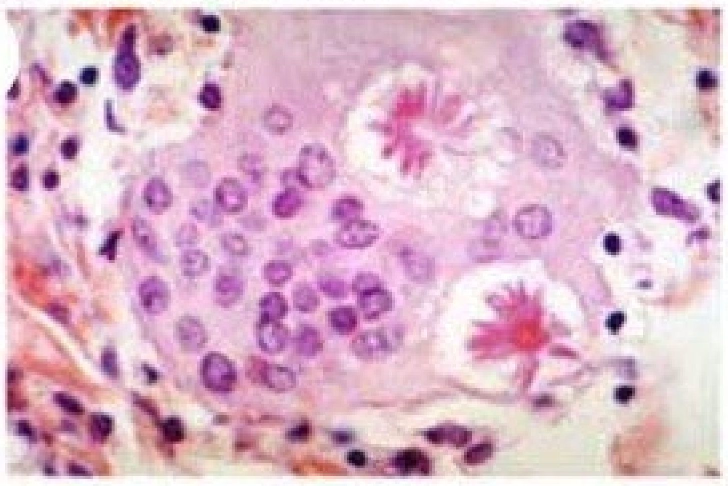


SARCOIDOSIS WITH NAKED GRANULOMA



SARCOIDOSIS - SCHAUMANN BODY

Schaumnann bodies are large basophilic concentric calcifications formed within the cytoplasm of giant cells.



SARCOIDOSIS - ASTEROID BODIES

These are stellate inclusions with numerous rays radiating from a central core that are present within the cytoplasm of giant cells.

2. TUBERCULOSIS

- aka Koch's disease
- Acid Fast & Caseous necrosis is d/t Mycolic Acid
- Virulence factor : Cord Factor

-Pathogenesis : Ag $\xrightarrow{\oplus}$ $CD_4 T_{H1}$ → IFN-γ → Granuloma formation
Caseating >> Noncaseating

- TUBERCULOSIS

Primary Tuberculosis

- pediatric age group
- Source of infection : Exogenous
- LN involvement is common
  U/L Hilar LN Enlargement
- calcification
  Pleural Effusion
  Erythema Nodosum
  Phlyctenalar conjuctivitis } ++++
- Pulmonary fibrosis
  Cavitation } Rare

Morphological Examination

1. GHON'S FOCUS
   Subpleural fibrocaseous Granuloma
2. GHON'S COMPLEX
   Ghon's Focus + Lymphatic & LN
3. Ranke's Complex
   Ghon's Complex + Areas of Fibrosis and calcification

Secondary Tuberculosis

(=Re-activation TB)

- Adults with ↓ immunity
  ↓
  Reactivation of TB foci
- ∴ Source : Endogenous
- LN involvement Rare
- calcification
  Pleural Effusion
  Erythema Nodosum
  Phlyctenalar conjuctivitis } + (rare)
- Pulmonary Fibrosis
  Cavitation } +++

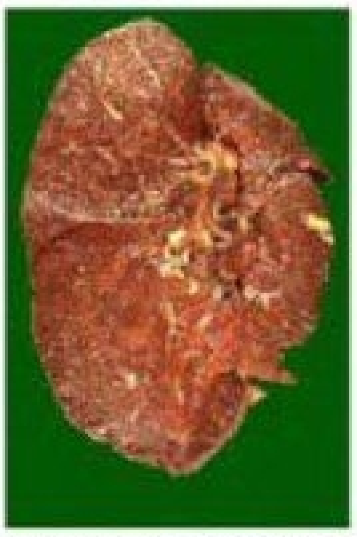
Morphological Examination

1. PUHL'S LESION
   Supraclavicular TB Nodule
2. ASSMAN FOCUS
   Infraclavicular TB Nodule
3. SIMON'S FOCUS
   TB nodule at apex of lung who's primary is else where in body
4. Miliary TB
   - it's d/t hematogenous spread
   - called as miliary becoz TB Nodules are of millet size (1-3mm)
   - 3 named Foci

PULMONARY VEIN
WEIGERT'S FOCUS
granuloma in subintimal part

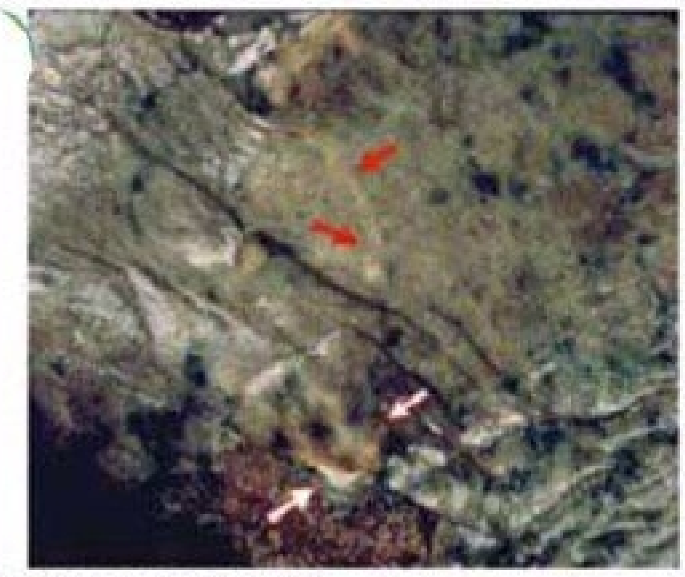
BRAIN
RICH'S FOCUS :
granuloma in cerebral Cerebral cortex

LIVER
SIMOND'S FOCUS



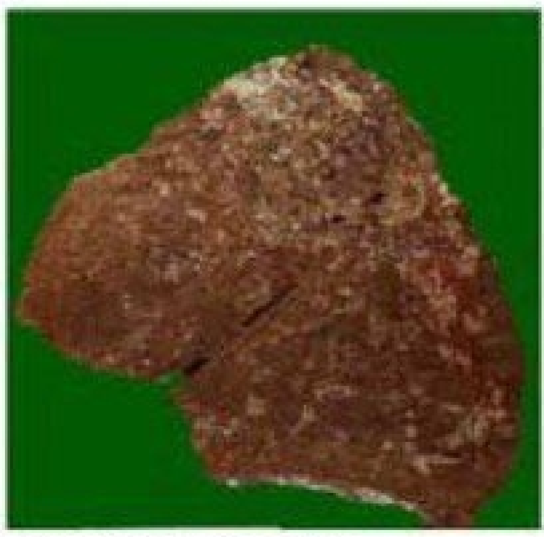
GHON'S FOCUS AND GHON'S COMPLEX

Subpleural fibrocaseous lesion (Consolidation) of lung parenchyma. Microscopically contains epithelioid granulomatous inflammation.



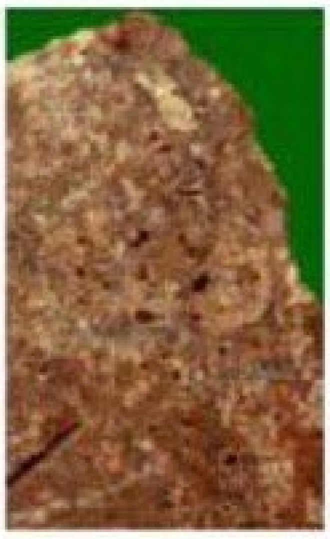
RANKE'S COMPLEX

Ghon's complex along with fibrosis and calcification known as Ranke's complex.



MILIARY TUBERCULOSIS

Multiple millimeter-sized nodules (arrows) are scattered throughout the lung parenchyma.



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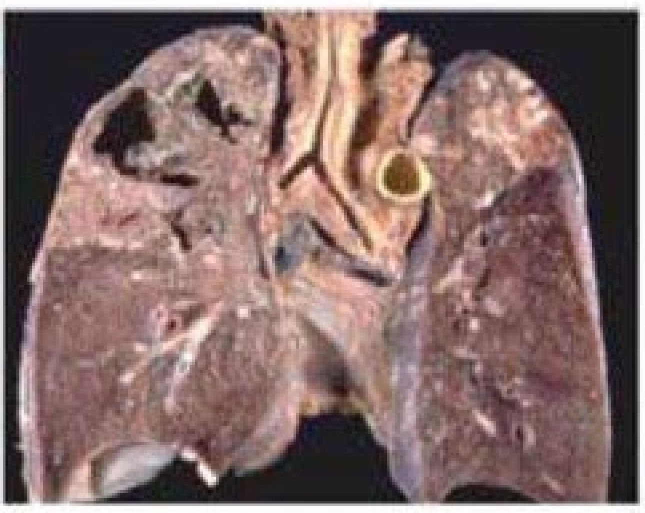
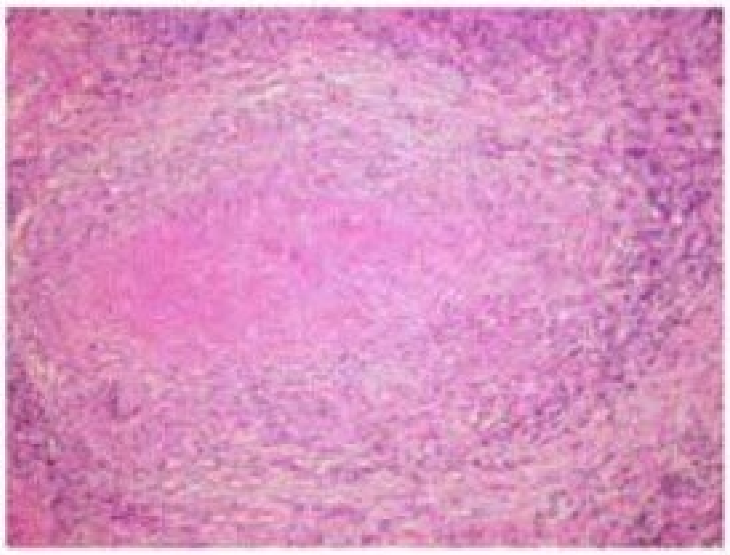


CAVITARY TUBERCULOSIS

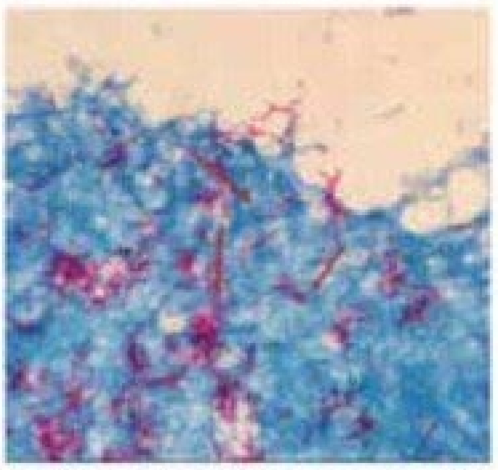
The apex of the right upper lobe shows prominent scarring and cavitation surrounded by consolidated and fibrotic pulmonary parenchyma.



TUBERCULAR GRANULOMA WITH CASEOUS NECROSIS

showing caseous necrosis and giant cells.

- Microscopic Examination :
  1. Caseous Necrosis
  2. Granuloma with FBGC & LGC
  3. Acid Fast Bacilli - Stain (AFB Stain)
     pink bacilli : beadded appearance



ACID FAST STAIN OF MYCOBACTERIUM TUBERCULOSIS (MTB)

Red rods are acid fast Mycobacteria bacilli. They have cell wall with lipids including fatty acids, specifically mycolic acid, making them resistant to phagocytic destruction, and acid fast.

Congenital TB : MC Site

For Primary ↓
Liver

Overall ↓
Liver

HYPERSENSITIVITY PNEUMONITIS

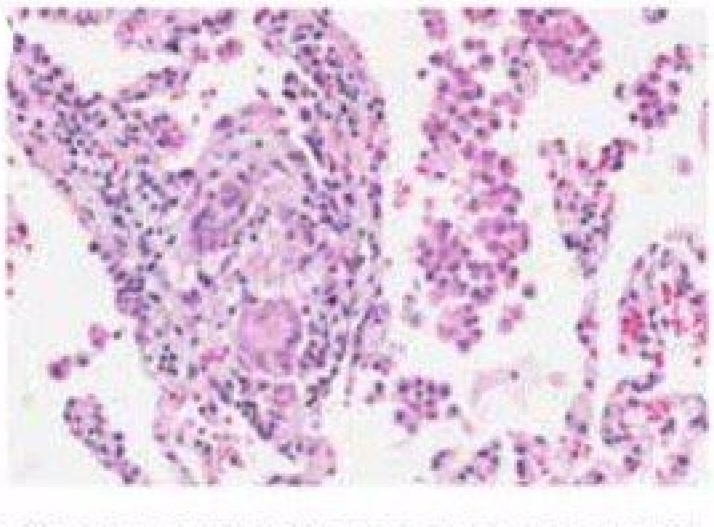
- aka Extrinsic allergic alveolitis
- immunologically mediated disorders d/t inhaled aerosols & antigen

Eg: Bagassosis : From sugurcane

Farmer's lung : d/t actinomycetes

Silo-filler's disease : d/t fermentation of Silage
↓
production of fumes of Nitrous & Nitric oxide

- Pathogenesis : immune complex mediated granulomatous inflammation
  (Both Type IV > Type III HSR)



DESQUAMATIVE INTERSTITIAL PNEUMONIA

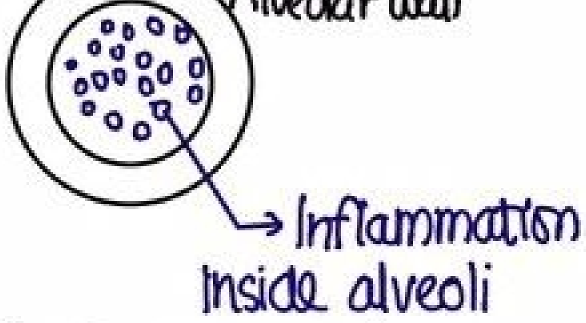
Lung shows the accumulation of large numbers of macrophages within the alveolar spaces and fibrous thickening of the alveolar walls.

PNEUMONIA

- It's infection & inflammation of Lung parenchyma
- 2 types

TYPICAL

* C/f : ↑↑ Signs & symptoms
  - Fever, Cough
  - TLC ↑↑
  - Chest X-Ray : consolidation
* Pathology :
  a/w congestion with consolidation
  ↓
  d/t Alveolar exudates



* MCC : Strept. pneumonia

BRONCHOPNEUMONIA

* patchy consolidation
* MCC : Strp- pneumonia
* Immunity ↑↑

LOBAR PNEUMONIA

* Lobar consolidation
* MCC : Strep.pneumoniae
* Immunity ↓↓

↓

LAENNEC'S STAGING

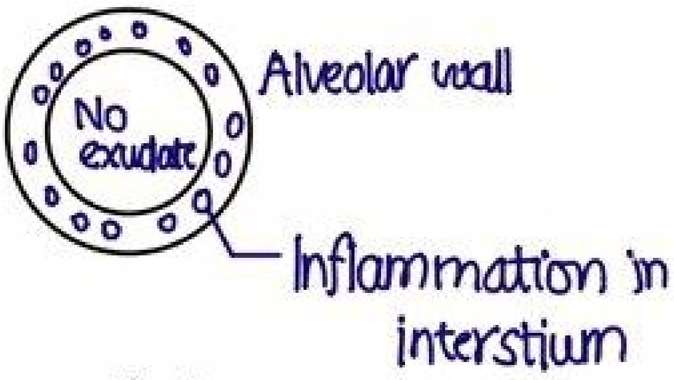
1. Stage of Congestion :
   Capillary congestion + ↑↑ Bacteria
2. Stage of Red Hepacitisation
   Hemorrhage + Neutrophilic exudates
3. Stage of Grey Hepatisation
   d/t grey coloured fibrinous exudates
4. Stage of Resolution

ATYPICAL

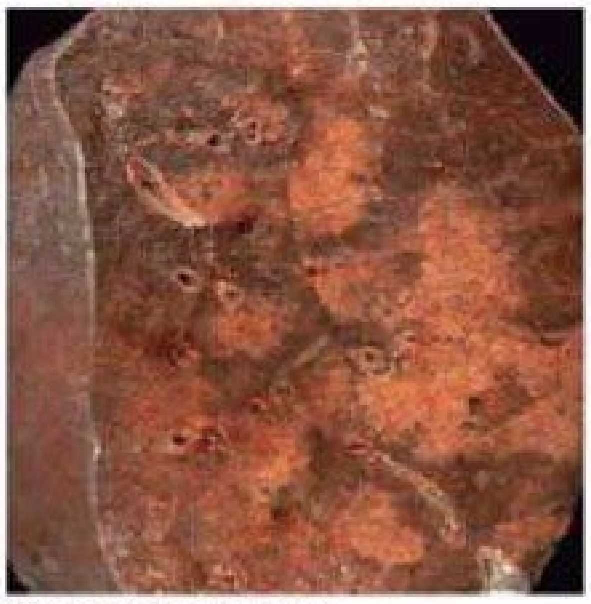
* C/f : Mild / Absent

  milder / absent

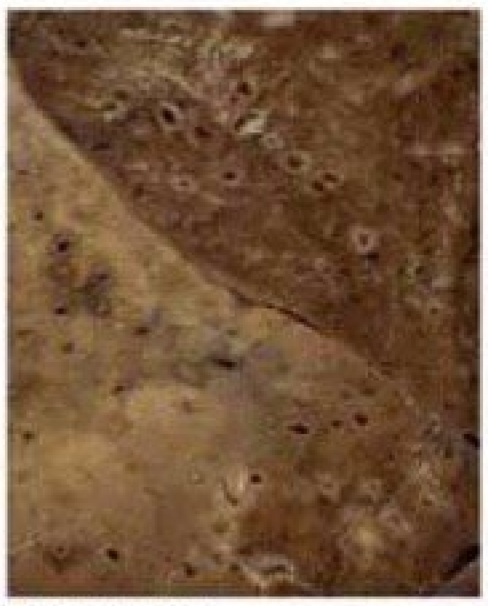
* Pathology :
  Congestion with no consolidation
  ↓
  No Alv. exudates



* MCC : Virus > Bacteria
  MCC : Mycoplasm inf.
* Giant cells ⊕
  Eg : Warthin Finkeldey GC of Measles virus
  causing Head't's Pneumonia



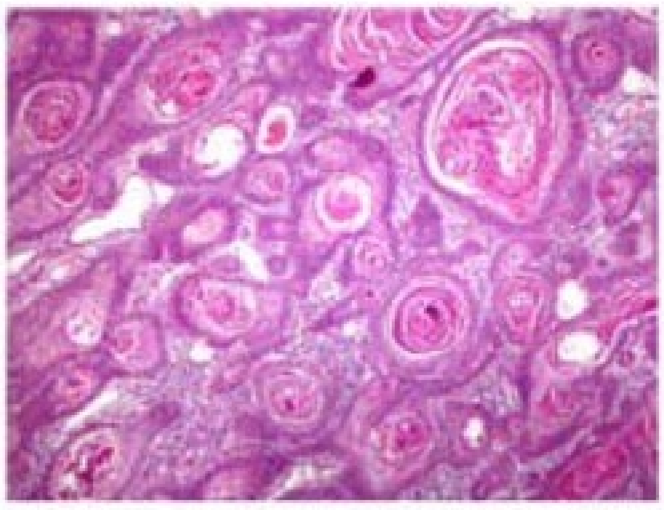
BRONCHOPNEUMONIA
Lung showing patchy consolidation (paler areas) of this lung



LOBAR PNEUMONIA
Entire left lower lobe is consolidated and in the stage of red hepatization. Upper lobe is normally expanded.

LUNG CANCERS

- MC Cancer causing death in adults : Lung cancers
- Various etiology :
  - i. Smoking MC a/w Squamous Cell Carcinoma
    M. Strongly a/w Small Cell cancer of Lung
  - ii. Radiation Exposure (Nickel & Cadmium)
  - iii. Asbetosis
- MC Lung cancer : Metastases
  - MC 1^0 Tumor for Metastases children : Osteosarcoma > Wilm's Tumor
  - MC 1^0 Tumor for Metastases adults : Breast Cancer
- MC 1^0 Tumor in Children : Carcinoid
  MC Benign Tumor in children : Inflammatory Myofibroblastic Tumor
- MC 1^0 Tumor in adults : Adenocarcinoma (in world)
  Sq. cell carcinoma (in india)
  MC Benign Tumor in adults : Hemartoma.

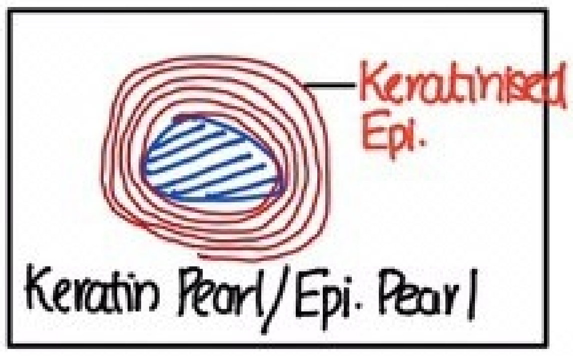


SQUAMOUS CELL CARCINOMA WITH KERATIN PEARL

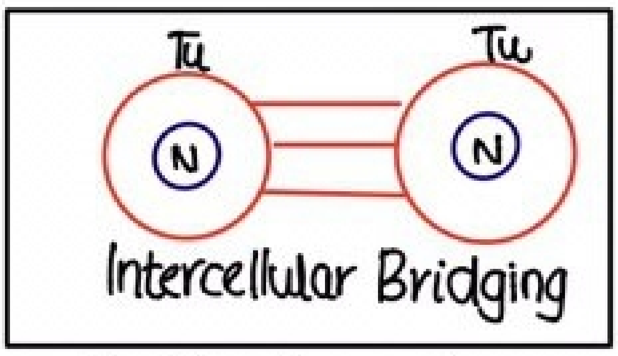
Well differentiated type of Squamous cell carcinoma will have presence of keratin or epithelial pearls.

1. SQUAMOUS CELL CARCINOMA OF LUNGS

- MC cancer a/w Smoking
- Location : Hilum
- MC a/w Hypercalcemia &
  Cavitation
  Pancoast Syndrome : MCC is Sq. CC
- M/E :
  - Well differentiated



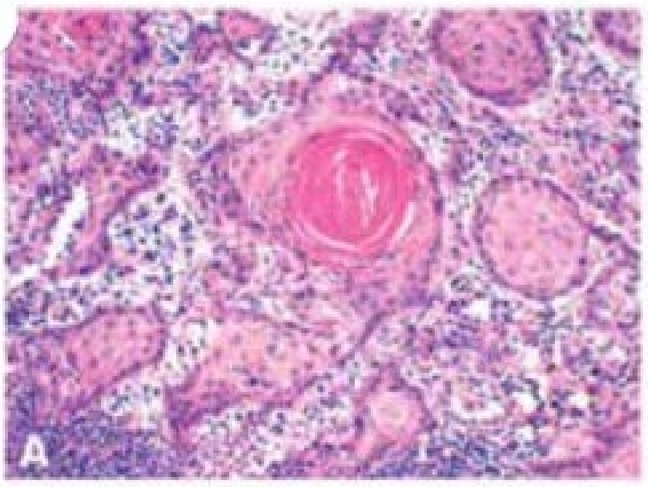
  - Moderately differentiated



* No Keratin pearls

  - Poorly differentiated

* No Keratin pearl
* No Intercellular Bridging
* IHC : CK ⊕ve
  p40 & p63



SQUAMOUS CELL CARCINOMA WITH KERATIN PEARL

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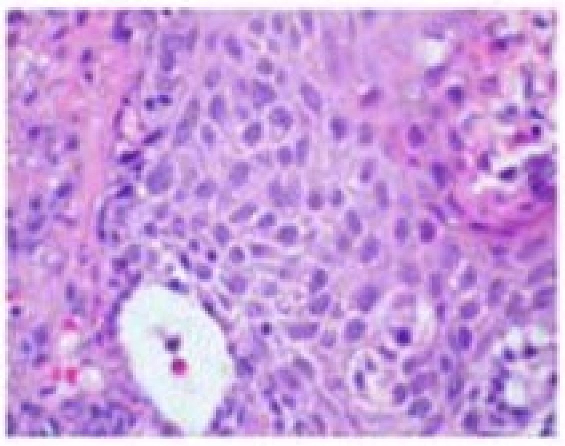
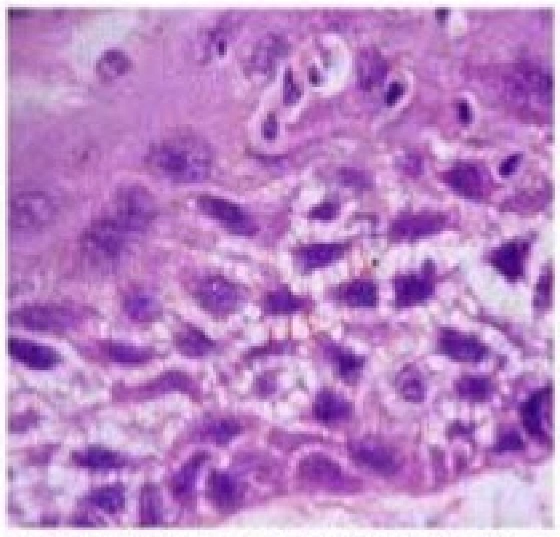


SQUAMOUS CELL CARCINOMA (MODERATELY DIFFERENTIATED TYPE) WITH INTERCELLULAR BRIDGES.

Moderately differentiated type of Squamous cell carcinoma will have presence of intercellular bridging.



SQUAMOUS CELL CARCINOMA (MODERATELY DIFFERENTIATED TYPE) WITH INTERCELLULAR BRIDGES.

Moderately differentiated type of Squamous cell carcinoma will have presence of intercellular bridging.

2. ADENOCARCINOMA OF LUNGS

- MC Lung cancer seen in females & non-smokers
- Location : Peripheral
- Adenocarcinoma In-situ (Bronchiolo alveolar carcinoma)
  - * Origin : • Clara cells of Terminal Bronchioles
    - • Type-II Pneumocytes
  - * No metastases & Good prognosis

    bcoz it's growing along Alveolar septa

    ↓

    No invasion to pleura, BV, Lung Parenchyma

    ↓

    ∴ called Lepidic pattern (Butterfly sitting on fence)
- Aerogenous spread is common (Lung → Lung)

Adenocarcinoma
- Mucinous
  - MC a/w Aerogenous spread

    ↓

    giving rise to lobar pneumonia like presentation
- Non-mucinous

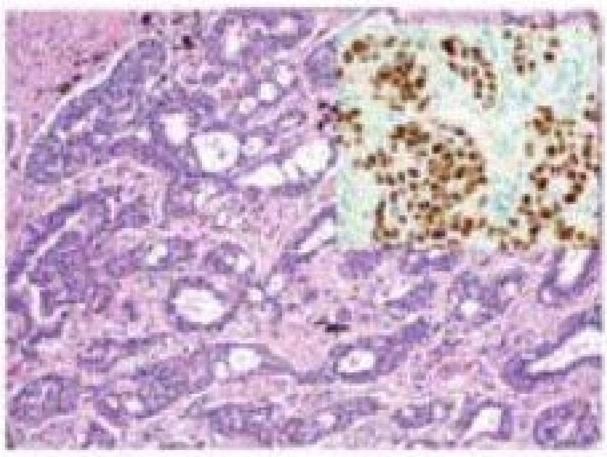
- Metastasis is wider & earlier. ∴ Adenocarcinoma have poorer prognosis than Sq.C.C
- Paraneoplastic Syndrome : Rare
  - • Gynacomastia
  - • Trosseau's Sign (Migra. sup. Thrombo phlebitis)
- M/E : i) Glandular pattern

  confirmed by IHC : TTF-1

  Napsin-A

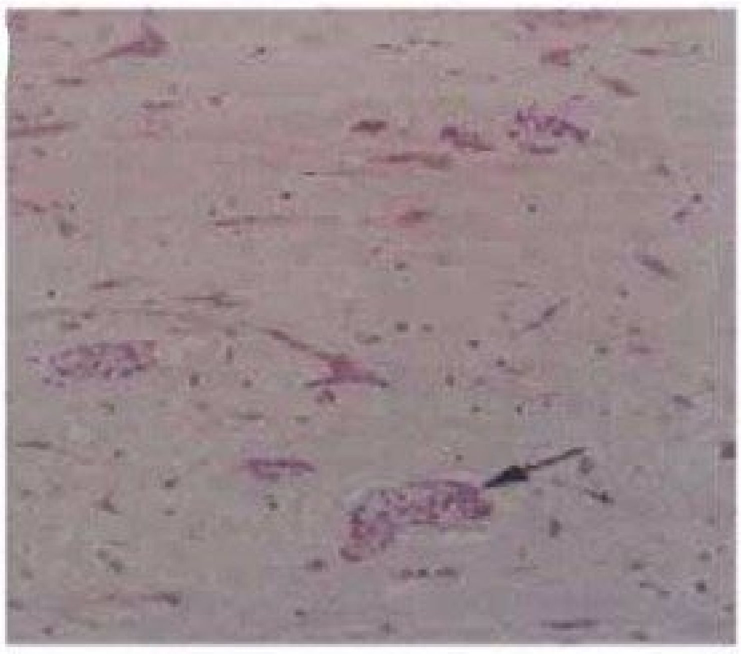
  CK-7 +

  CK-20 −



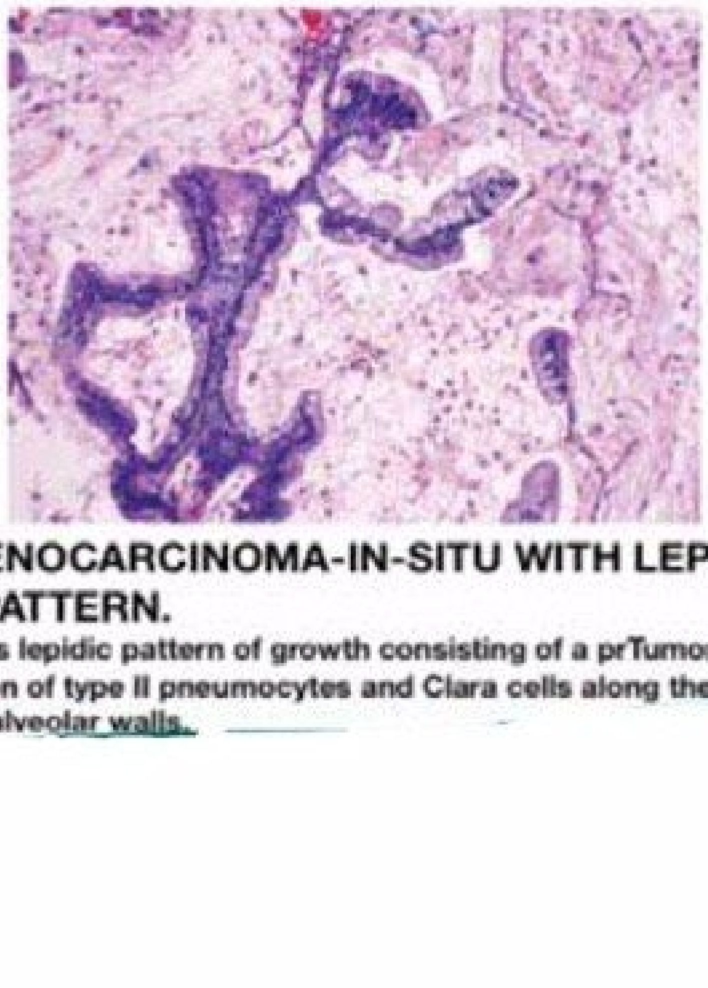
ADENOCARCINOMA

Gland-forming adenocarcinoma; inset shows thyroid transcription factor 1 (TTF-1) expression, as detected by immunohistochemistry.



LEPIDIC CELLS

in cardiac Myxoma.



ADENOCARCINOMA-IN-SITU WITH LEPIDIC PATTERN.

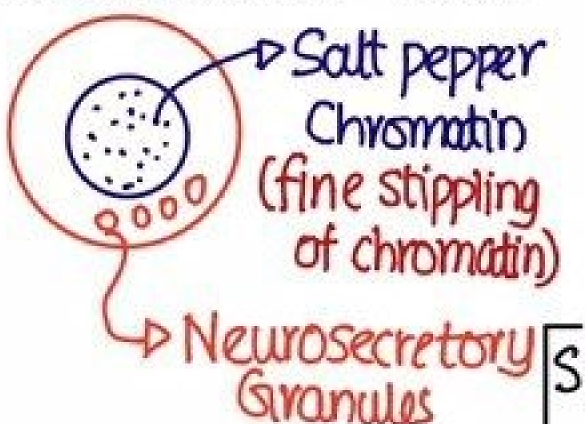
shows lepidic pattern of growth consisting of a prTumoroliferation of type II pneumocytes and Clara cells along the surface alveolar walls.

3. NEUROENDOCRINE TUMOR OF LUNG

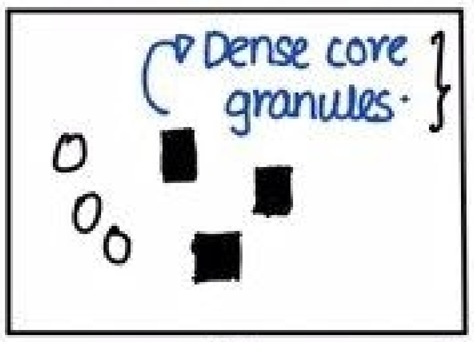
(A) SMALL CELL CARCINOMA

- Any neuroendocrine Tumor

M/E :



- E/M :



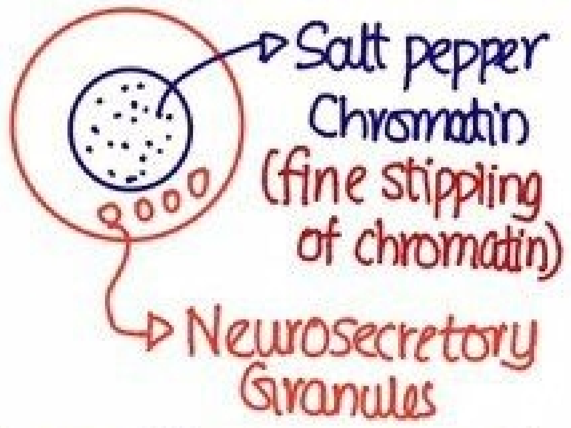
} Neurosecretory granules

Store [• Chromogranin • Neurofilament • Bombesin • Synaptophysin • Leu-7]

(A) SMALL CELL CARCINOMA

- Strongly a/w Smoking
- Location : Hilum/peripheral
- Superior Venacaval syndrome MC a/w SCC of Lung
- MIE :

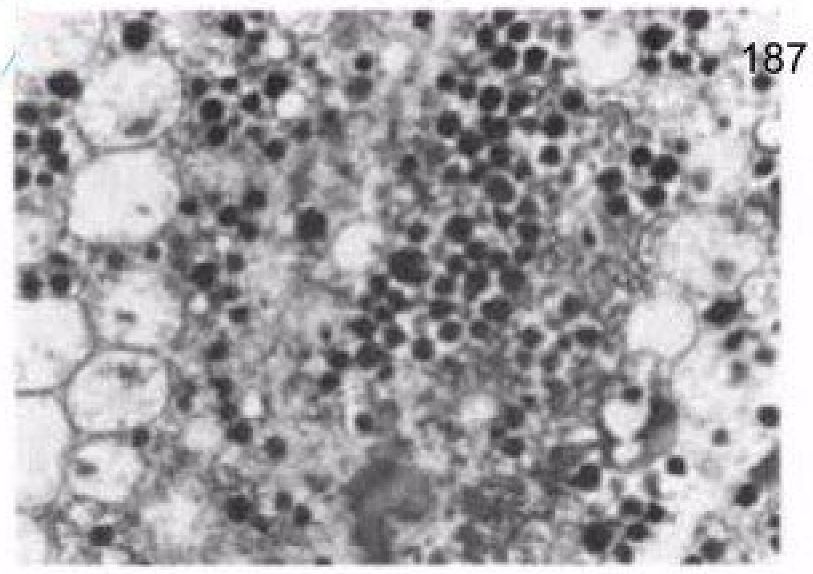
I



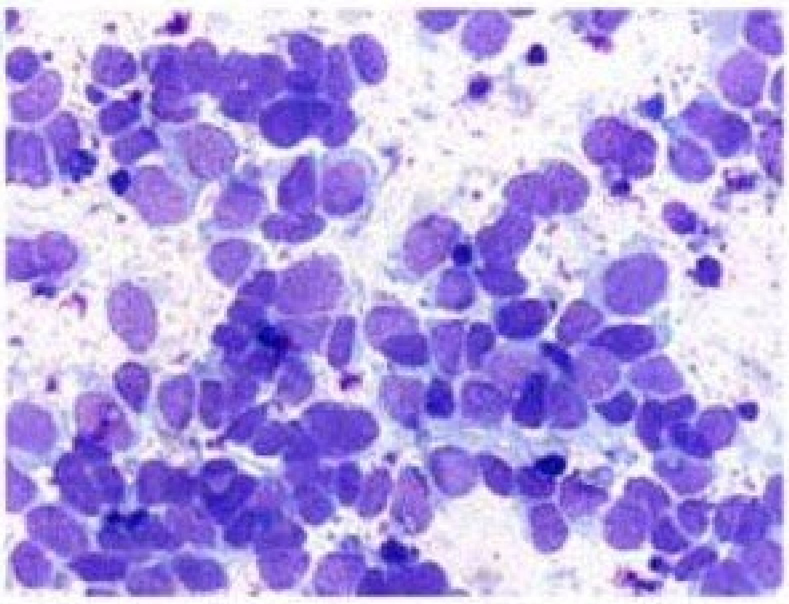
II Basophilic staining of Blood Vessal wall
↓
Azzopardi effect

III Nuclear molding → Nucleus.

- IHC : same as above
- EM : dense core granules



NEUROSECRETORY GRANULES (ELECTRON MICROSCOPY)
Dark dense core granules are seen.



SMALL CELL CANCER LUNG
Showing uniform cytologic features with finely granular nuclei with finely granular chromatin (Salt and pepper type chromatin).

DESMOSOMES OR TONOFILAMENT

Secretory RER → Adenocarcinoma

Neurosecretory granules → Small Cell Ca. of Lungs

- Paraneoplastic Syndrome is MC associated with Small Cell Ca. of Lung
  - MC PNS : SIADH ≫ Cushing Syndrome
  - Hyper calcemia ; Sq. CC ≫ Adenocarcinoma
  - Lambert Eaton myasthenia
- WORST PROGNOSIS

(B) TUMORLET

- Tumorlet v/s Carcinoid

Tumorlet	Carcinoid
↓	↓
Size <5mm	Size >5mm

- No Necrosis
  No mitosis
- d/t Chronic inflammation & scarring
  ↓
  Type-II pneumocyte hyperplasia
  ↓
  Tumorlet

(C) BRONCHIAL CARCINOID

- Female 40-60yrs
- MC presentation : Hemoptysis
- Neuro-endocrine Cell are
  MC site GIT ≫ Lung
- MC site of Carcinoid : GIT ≫ Lung
  ↓
  Appendix ≫ Ileum
  Lung > Ileum
- Usually asymptomatic
  Symptoms when carcinoid syndrome is present
  ↓
  - occurs when metast. to liver
  - symptoms are d/t Serotonin
    ∴ • ↑BP • Hemoptysis
    • ↑ Skinflushing • Diarrhea.

LUNG-CARCINOID : MC SITE FOR METASTASES: LIVER

TYPICAL (MC)	ATYPICAL
* C/F : slow growth less metastases	* C/F : Faster growth ↑↑ metastases
* Labfindings: ↑ serotonin ↑ Chromogranin-A	* Lab findings (Blood) Ⓝ Serotonin Ⓝ Chromogranin-A
* Urine examination ↑ 5· Hydroxy Indole Acetic Acid	* Urine examination ↑ serotonin ↑ 5 Hydroxy tryptophan
* Histo pathology ↑ Mitotic figures (<2 / 10HPF) Necrosis ⊖ Hemorrhage ⊖	* Histopathology >2-10 Mitotic figures /10HPF ↑ atypical MF Necrosis ⊕ Heamorrhage ⊕

for more notes,join our telegram channel, "latest neet pg notes 2020" or join via link " t.me/latestpgnotes"

KIDNEY & URINARY BLADDER

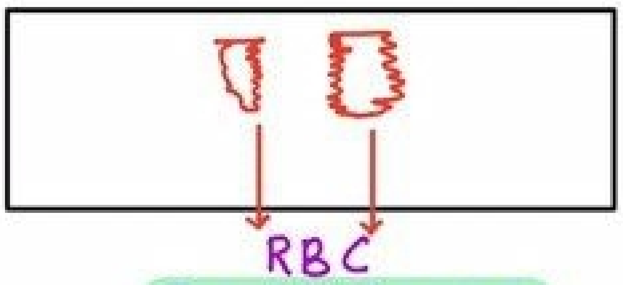
1. Glomerular Injury
   - Proteinuria
   - Hematuria
   - Cast in urine
2. Tubulo-interstial
   - Salt-loosing nephritis
3. Vasular
4. Neoplasm

HEMATURIA

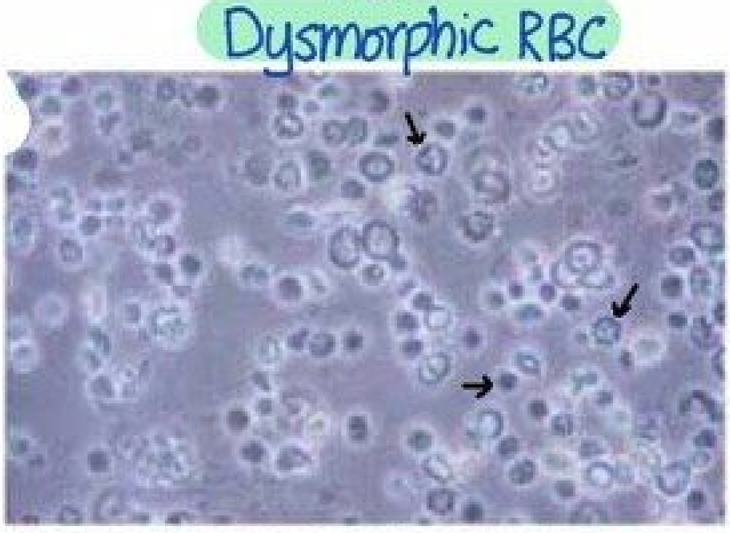
- Presence of RBCs in urine
  >3 RBCs / high Power field (HPF) for >3 consecutive times 1 week apart
  (OR)
  >1000RBCs/ml of urine
- Source of injury :

GLOMERULAR

* MCC : IgA Nephropath
  PSGN
* Urinary Smear



Dysmorphic RBC

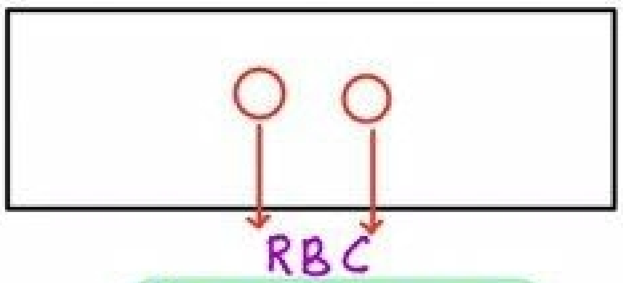


DYSMORPHIC ERYTHROCYTES

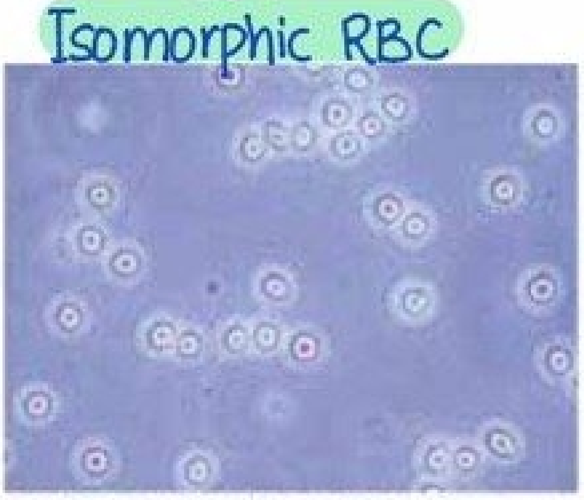
These dysmorphic erythrocytes vary in size, shape, and hemoglobin content and reflect glomerular bleeding e.g. IgA nephropathy, Poststreptococcal glomerulonephritis

EXTRAGLOMERULAR

* MCC : Renal Stones
  (=Idiopathic Hypercalciuria)
* Urinary Smear



Isomorphic RBC



ISOMORPHIC ERYTHROCYTES

These erythrocytes are similar in size, shape, and hemoglobin content. Isomorphic cells reflect nonglomerular bleeding from lesions such as calculi and papillomas or hemorrhage from cysts in polycystic renal disease.

PROTEINURIA

- Normally proteins in urine : <150 mg/day
  - >2/3rd : Tamm Horsfall Protein
    - ↓ derived from Thick ascending loop of Henle

Glomeruli allows ultrafiltaration of protein

- SIZE
  - ✓ Size <4 Å : Freely Filtered
  - >8 Å : Not filtered
- CHARGE
  - ✓ Negatively charged : Not filtered
    - → Eg: Albumin
    - → Because there is negatively charged
      - a) Endothelium d/t Sialoprotein
      - b) BM d/t Glycoproteins

Albumin appears earliest in Proteinuria
∵ of Smallest size & Molecular weight

PROTEINURIA

On the basis of clearance ratio = $\frac{IgG}{\text{Albumin or transferrin}}$

SELECTIVE

⇒ $\frac{IgG}{Albumin} < 0.1$

- defect is with charge
- not a/w SIZE
- MCC : Minimal change disease
- both γ globulin & albumin comes out

NON-SELECTIVE

⇒ $\frac{IgG}{Albumin} > 0.2$

- d/t defect in charge & size
- Cause : All glomerular pathology

PROTEINURIA

NEPHRITIC SYNDROME

- Pt with h/o HT^n ↓ Hematuria ↓ RBC-Casts } ++++
- Proteinuria : <3.5 gm/day

NEPHROTIC SYNDROME

- Pt with h/o HT^n ↓ Hematuria ↓ RBC-Casts } +
- Massive Proteinuria (>3.5 g/day)
- HYPER LIPEDIA ← d/t loss of Lipoprotein
  - ↓
- LIPIDURIA
  - ↓
- LIPID CAST / WAXY CAST

* Milder Edema
d/t Na^+ & H_2O Retension

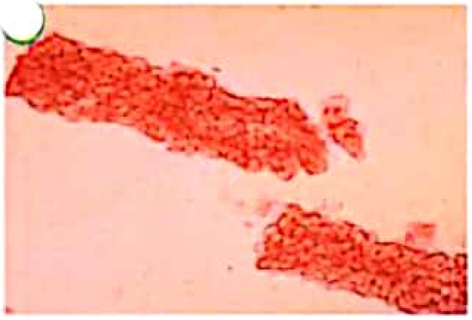
* MOST COMMON CAUSE:
In Pediatric : PSGN
in Adults : IgA Nephropathy
overall : IgA Nephropathy

* Loss of Protein C,S & AT-III
∴ HYPERCOAGULABLE CONDITION
(d/t ↑ fibrinogen synthesis)
↓
∵ of inflammation of nephron as it's a Positive Acute phase responce Protein

* Severe Edema
d/t Na^+ & H_2O Retension ≫ Hypoproteinemia

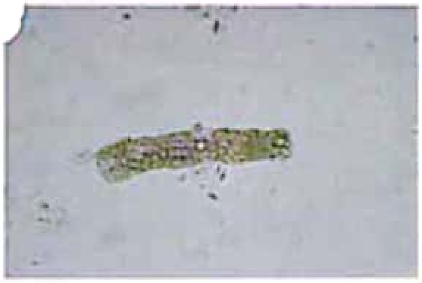
* MOST COMMON CAUSE:
i. Primary (Unknown)
in pediatrics : MCD
In adults : FSGS
in elderly : Membra. GN
overall : FSGS
ii. Secondary (d/t systemic illness)
MCC : Diabetes Mellitus

OVERALL MCC of Nephrotic Syn.
Diabetes Mellitus



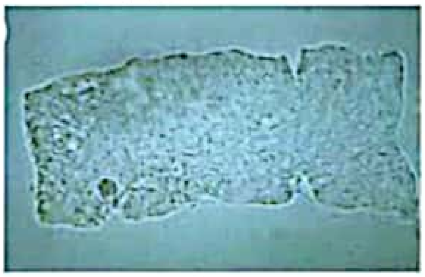
RBC CASTS

Red Blood Cells within the cast.
Seen in Nephritic syndrome, Pyelonephritis, and Urinary tract injury.



FATTY CASTS

Formed by the breakdown of lipid-rich epithelial cells, these are hyaline casts with fat globule inclusions.
Seen in Tubular degeneration, Nephrotic syndrome, and Hypothyroidism.



WAXY CASTS (RENAL FAILURE CASTS)

Edges are sharp and there are "cracks" in such casts.
- End product of cast evolution which is suggestive of very low urine flow associated with severe, longstanding kidney disease such as renal failure.

Seen in Nephrotic syndrome and Chronic renal failure.

Most commonly Urinary cast forms in DCT

Genetic Basis of Nephrotic Syndrome

1) NPHS-1 Gene [Chr. 19q]
↓
Protein : Nephrin
↓
mutation /defect
↓
i) Congenital Nephro. Synd [FINNISH TYPE]
ii) FSGS

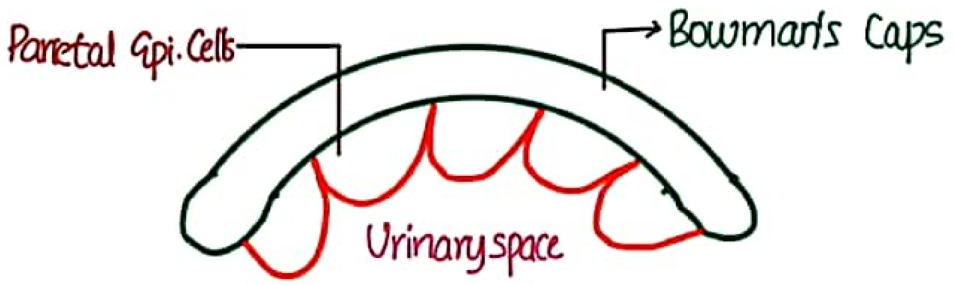
2) NPHS-2 [Chr. 1q]
↓
Protein : Podocin
↓
defect /mutation
↓
i) Idiopathic Steroid Resistant Nephrotic Syndrome
ii) Autosomal Recessive FSGS

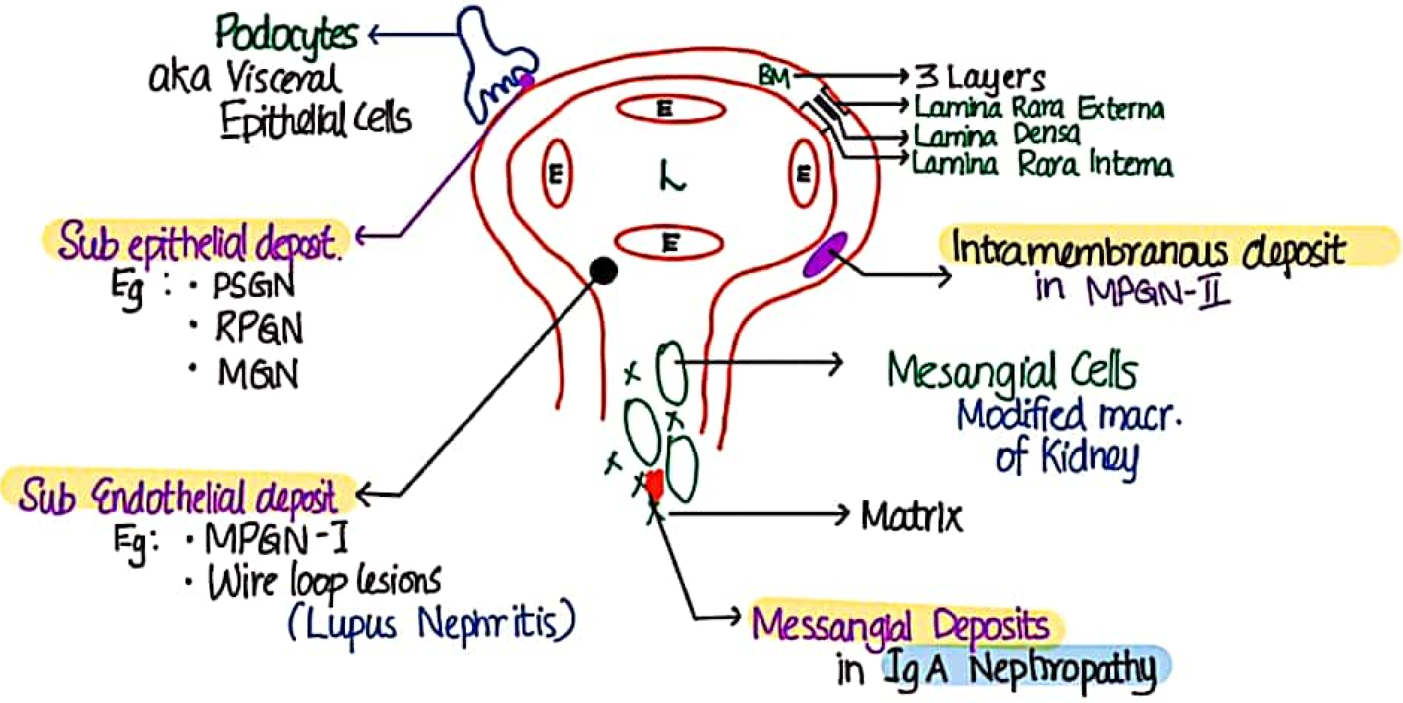
3) α - Actin - 4
↓
Mutation
↓
Autosomal Dominant FSGS

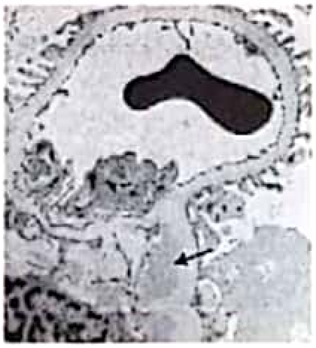
4) TRPC-6 Gene
↓
mutation
↓
Adult onset FSGS

Scanned with CamScanner

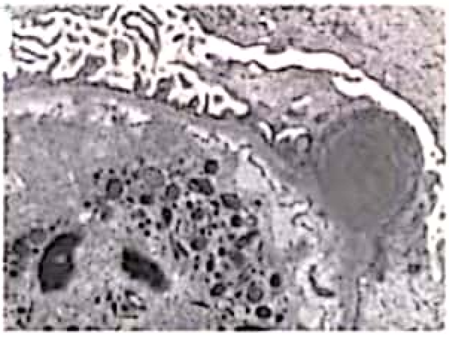
ELECTRON MICROSCOPY OF KIDNEY



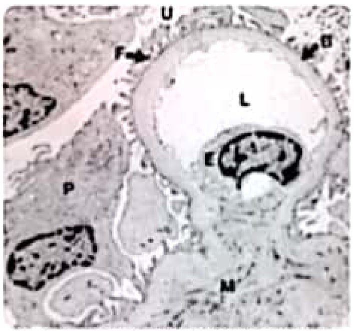




IMMUNOGLOBULIN A NEPHROPATHY.
An electron micrograph demonstrates prominent dense deposits in the mesangial matrix (arrow).



ACUTE PROLIFERATIVE GLOMERULONEPHRITIS.
lectron-dense subepithelial "hump".



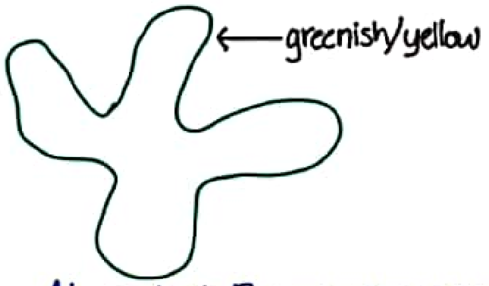
NORMAL GLOMERULAR CAPILLARY (ELECTRON MICROSCOPY)
[illegible]

In EM deposits are Dark, homogenous, grey colour

Scanned with CamScanner

IF MICROSCOPY

LINEAR PATTERN
- Suggestive of Ab Mediated

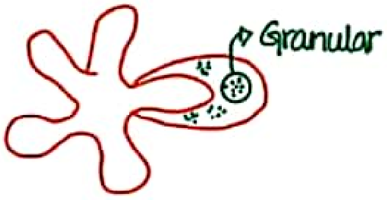


Ab against Basement membrane
- aka Ribbon like appearance

↓

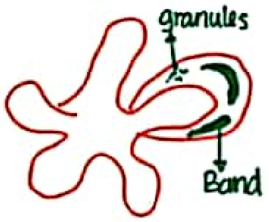
Good Pasteur syndrome (IgG/C3)

GRANULAR
- Suggestive of Immune complex mediated



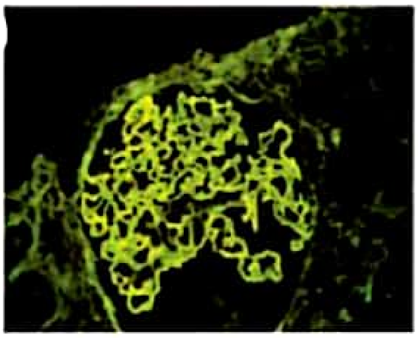
- Eg:
  - PSGN
  - Membranous GN
  - MPGN-I

BAND-LIKE
- Dense immune complex mediated

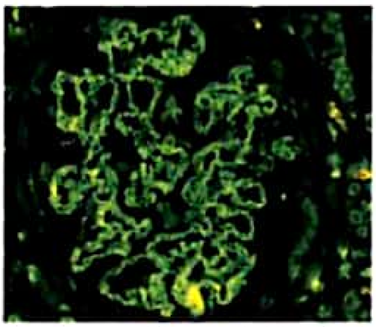


↓

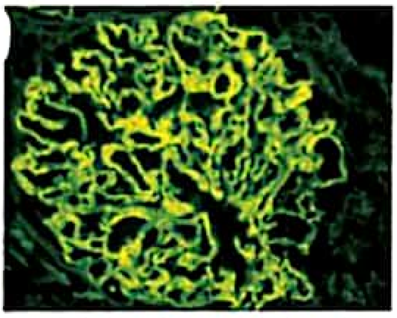
Seen in MPGN-II



ANTI GBM DISEASE (IMMUNOFLUORESCENCE MICROSCOPY)
Linear immunofluorescence characteristic of classic anti-GBM disease e.g. Goodpasture syndrome.



ACUTE PROLIFERATIVE GLOMERULONEPHRITIS (IMMUNOFLUORESCENCE MICROSCOPY)
Granular immunofluorescence characteristic of immune complex mediated nephritis.



MEMBRANOUS GLOMERULONEPHRITIS
(Immunofluorescence microscopy) Showing granular deposits (Immune complexes) of immunoglobulin G (IgG) outlining Jhe glomerular capillary loops.

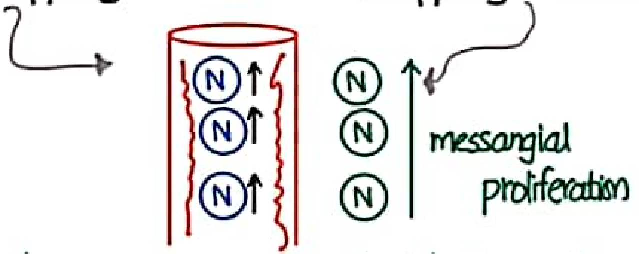
POST-STREPTOCOCCAL GLOMERULO NEPHRITIS · PSGN

- New Name : Acute Proliferative GN
- Clinical Features :
  - Children (MC) (5-15yrs)
  - group A β-hemolytic streptococcal infection
    - ↓ Pharyngitis
    - ↓ Skin infection/Impetigo
  - Pt with h/o Pharyngitis
    - after 1-3 days → IgA Nephropathy
      - ⇒ Recurrent Hematuria ⊕
      - ⇒ initially ↓ C3 & then Normalised after 6-8wks (~2mont)
      - Transient hypocomplementenimla
    - ↓ Hematuria : Cola coloured urine
    - after 1-3wks → PSGN
      - ⇒ Single episode of Hematuria
      - ⇒ C3 level is normal

- Serology : Anti-streptolysin O (ASO) Titre ≪ Anti-DNA Antibody
- Light Micro. : Glomeruli : Hypercellular

d/t

Endocappillary Proliferation — Exocappillary Proliferation



- Electron microscopy : Immune complex mediated Glomerulonephrites (Type-III HSR)
  All types of deposits are seen.
  MC type : Subepithelial deposit
- IF : Granular Pattern of IF
- Prognosis is good
  ∵ Chronic Renal Failure is least commonly seen
  MCC of CRF in Glomerulo nephritis : RPGN

IgA Nephropathy

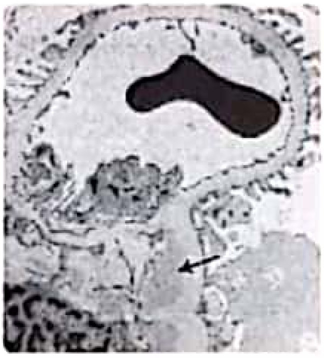
- aka Berger's disease
- Commonly in Pediatric ; 5-15 yrs
- MC Type of Glomerulo nephritis ; Adults & overall
- MCC of Hematuria (Gross, Microscopic & Recurr. Hematuria)
- d/t : Pharyngitis, Celiac ds, Hepatitis } $\xrightarrow{1\text{-}3\ days}$ HEMATTURIA

→ Pathogenesis : ↑ IgA (mucosal sectrions)

isotype → IgA₁, IgA₂

IgA₁ ↓ Nephritogenic

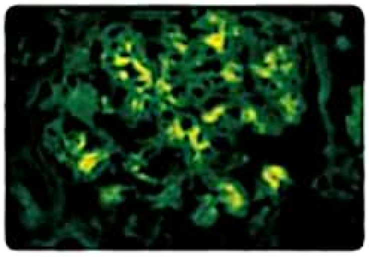
↓ Causes Messangial destruction



IMMUNOGLOBULIN A NEPHROPATHY.
An electron micrograph demonstrates prominent dense deposits in the mesangial matrix (arrow).

Mesangial Deposits
deposits are IgA₁ ; IgG/M ; C₃ → N

- Light microscopy : Messangial Hypercellularity
- Electron microscopy : Mesangial deposits
- Immuno. Flo. (IF) : Patchy messanglal deposits



IMMUNOGLOBULIN A NEPHROPATHY.
An immunofluorescence microscopy demonstrates prominent dense deposits in the mesangial matrix.

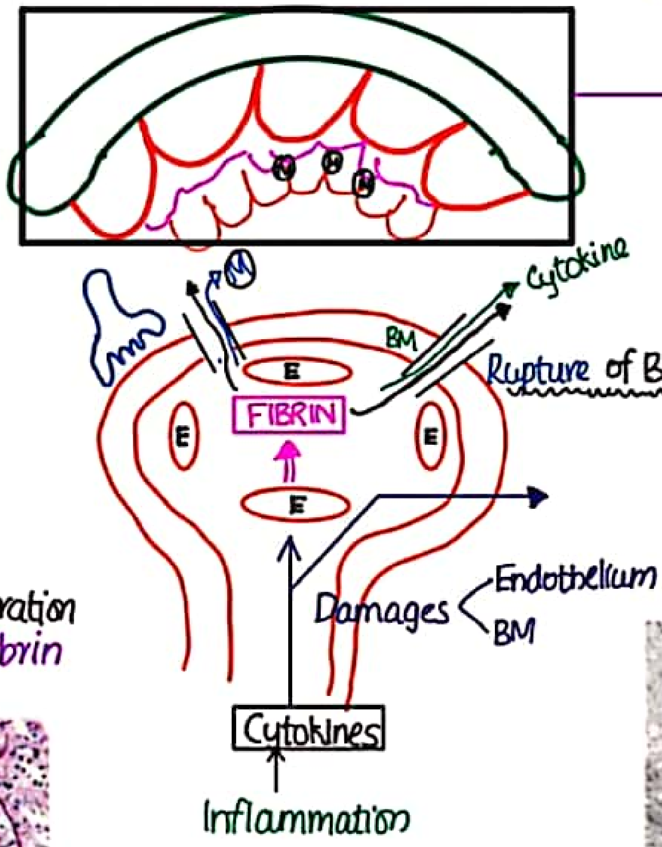
Scanned with CamScanner

Rapidly Progressive GlomeruloNephritis

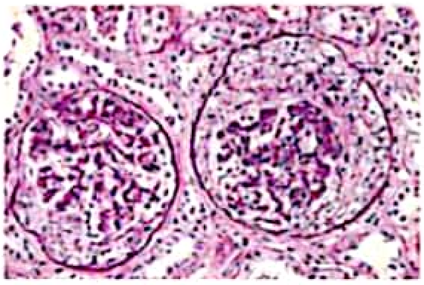
- aka CRESCENTRIC Glomerulonephritis
  d/t presence of CRESCENTS
  - → i. Most charachteristic Histologic finding of RPGN
  - ii. No. of crescents correlate to the prognosis
  - iii. Made up of :
    Parietal Epi. Cells + $\underbrace{\text{Fibrin}}_{\text{Most important Factor}}$ + Mononuclear Cell

- Pathogenesis of crescent formation :

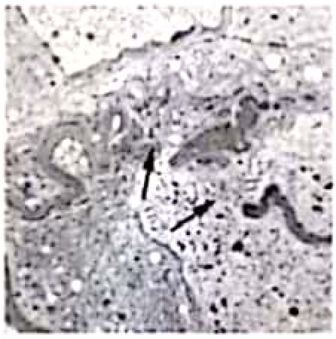
Endothelial damage
↓
Formation Fibrin
↓
Cytokine, Fibrin & infl. cells
(Monocytes)
Leak into urinary space
↓
Fibrin get deposited on
parietal cells
↓
Parietal epithelial proliferation
Sticking to each other ͞c Fibrin



Rupture of Basement Membrane
↓
On EM
Wrinkling of B.M



CRESCENTIC GLOMERULONEPHRITIS (PAS STAIN)
Showing collapsed glomerular tufts and the crescent-shaped mass of proliferating parietal epithelial cells and leukocytes internal to Bowman capsule.



CRESCENTIC GLOMERULONEPHRITIS
Electron micrograph showing characteristic wrinkling of glomerular basement membrane with focal disruptions (arrows).

Classification of RPGN :

TYPE-1
anti-GBM
- Pathology :
  IgG Ab ⟶ BM
  (Type IV : α_3 chain Collagen)
  Eg : Good Pasteure Syndrome
  (Type II HSR)
  First Lungs then Kidney
  MCC of Death : Renal Failure

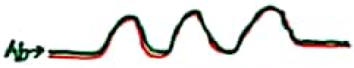
TYPE-2
Immune complex
- Henoch-schonlein purpura
- SLE (lupus Nephritis)

TYPE-3
Pauci-immune (MC ;>50%)
- On IF :
  there is no immune complex
- a/w ANCA
  (Anti neutrophilic Cytoplasmic Ab)

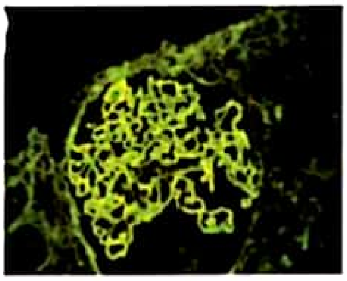
Scanned with CamScanner

TYPE-1

- On IF:



Linear or Ribbonlike



ANTI GBM DISEASE (IMMUNOFLUORESCENCE MICROSCOPY)

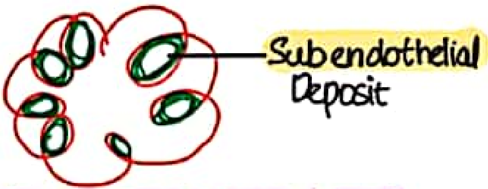
Linear immunofluorescence characteristic of classic anti-GBM disease e.g. Goodpasture syndrome.

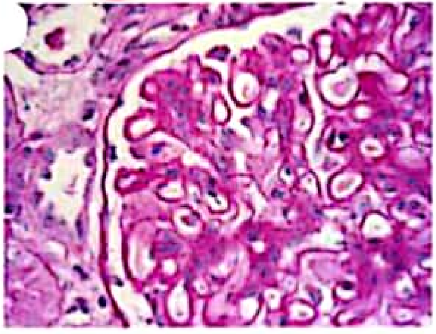
TYPE-2

- There are 6 classes of SLE

Best Prognosis → I : Minimal GN
II : Mesangial GN
III : Focan GN
worsening of Prognosis IV : Diffuse proliferative GN
V : Membr. GN
VI : Sclerosing Nephritis → Worst Prognosis

Wire loop lesions



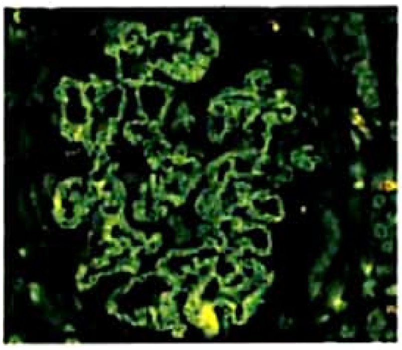


LUPUS NEPHRITIS (WIRE LOOP LESION)

Homogenous rigid thickening of capillary loop due to subendothelial deposits.

Wire loop lesions s/o
# active disease
Poor prognosis
# seen in
Class III, IV, V
MCC is Class IV

- On IF:
Granular IF



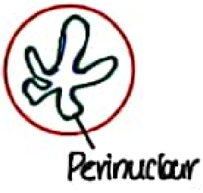
ACUTE PROLIFERATIVE GLOMERULONEPHRITIS (IMMUNOFLUORESCENCE MICROSCOPY)

Granular immunofluorescence characteristic of immune complex mediated nephritis.

TYPE-3

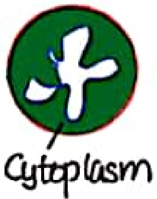
- ANCA

P-ANCA

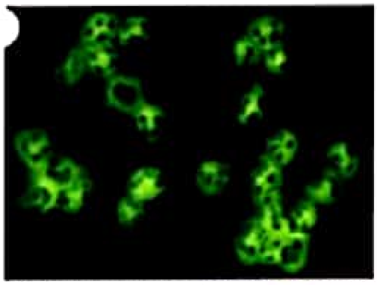


Seen in
- Microscopic Polyangitis
- PAN : No ANCA

C-ANCA



Seen in
- Granulomatosis with polyangitis
↓
70% : C-ANCA
25% : p-ANCA



C-ANCA BY INDIRECT IMMUNOFLUORESCENCE

Showing heavy staining in cytoplasmic area while multilobulated nuclei (clear zones) are non-reactive

Poor prognosis : RPGN
∵ of Rapid Renal Failure
MCC of CRF

Scanned with CamScanner

Alport Syndrome

- 5 - 20 yrs age group
- Clinical Features : 1. Eye
  - Anterior lenticonus
  - Subluxation of lens

  ii. Ear
  - Sensorineural Deafness

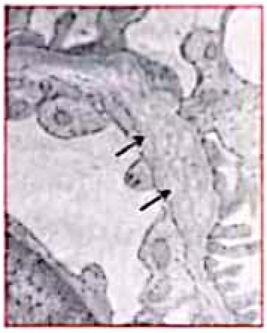
  iii. Kidney
  - Hematuria & Nephritis
- Genetics :

Autosomal << X-linked

AR
AD

XLD (MC pattern of inheritance: 85%)
XLR

- Pathogenesis : Defective assembly of collagen in BM
  In Autosomal variant : α_3, α_4 defective
  In X-linked variant : α_5 (MC) defective
- Light Microscopy & IF : No diagnostic finding
  ↓
  ∴ it's not antibody mediated
- On Electron microscopy : It's diagnostic
  Earliest = Thinning of B.M
  ↓
  irregular thickening
  ↓
  Rupture
  ↓
  Lamellated Healing by Lamina Densa
  also called as Basket Weave Appearance



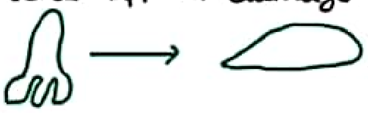
ALPORT SYNDROME
The lamina densa of the glomerular basement membrane is laminated (arrows) rather than forming a single dense band.

Minimal Change Disease - MCD

- MCC of Nephrotic syndrome in pediatric age group.
- Etiology : • Resp. infection
  • Immunisation
  • Lymphoma / Leukemia : MC Glomerular pathology : MCD
- Pathology : Immunological Reaction
  ↓
  ↑ Cytokine release
  ↓ Visceral Epi. cell damage
  ↓ loss of poly anion on BM

Scanned with CamScanner

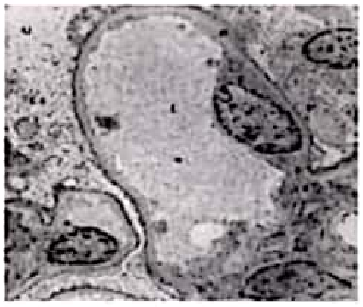
Visceral Epi. cell damage



loss of polyanion on BM
↓
PODOCYTES

Called as Fusion or Effasement of podocytes

- Clinical Features : Pediatric
  Massive selective Proteinuria : MC presentation
  No HT^n / Hematuria
- LM/ IF Microscopy : Non diagnostic
- aka Lipoid Nephrosis
  ∵ on LM Tubules with Lipid deposition
- EM : Diagnostic Effasement of Podocytes
  Basement Membrane : Normal
- Effasement of podocytes is seen in : MCD : Normal BM
  MGN }
  FSGS } BM damage
  MPGN }



MINIMAL-CHANGE DISEASE
(Electron microscopy) showing effacement of foot processes (arrows) and absence of deposits. (CL, Capillary lumen; M, mesangium; P, podocyte cell body).

Membranous Nephropathy

- MCC of Nephrotic syndrome in elderly.

MGN

PRIMARY (Unknown)
- MC

SECONDARY
- less common
- d/t
  i) Drugs : NSAIDS
  ii) Infection : • Hepatitis → B : MC in Pedia : MGN (overall)
  MC in adults : MPGN
  → C : MC a/w CRYOGLOBULINEMIA > MGN > MPGN-1
  • Syphilis }
  • Schistosomiasis } MC a/w MGN
  iii) Cancers : Breast
  Colon : MC a/w MGN

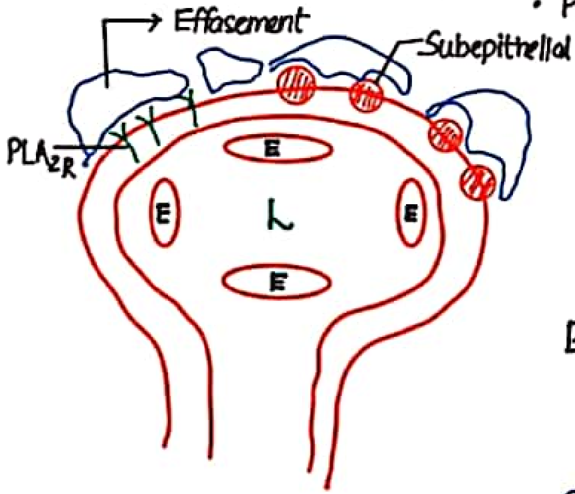
- Pathogenesis : d/t Immune complexes : Usually IgG$_4$ deposit
  ⇓
  Cytokines → Damage to BM & Visc. Epi. Cells
  ↓ Thickening ↓ Effacement

✳ Megalin [PCT Ag of mouse] : Used for experimental model of MGN
HEYMAN'S NEPHRITIS

✳ Phospholipase - A$_2$ Ⓡ corresponds to Megalin Ag on mouse
→ Biomarker of disease severity.

Scanned with CamScanner

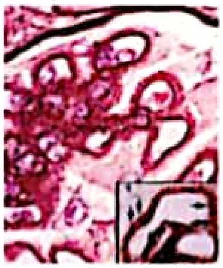
- Light Microscopy : • Capillary BM thickening due to immune complex deposition
  • No Rupture of BM
- IF : • Granular immunoflourescence
- Electron microscopy : • Effasement of foot process
  • Phospholipase A_2 ® on BM, behave like Ag



↓
form immune complexes
↓
Thickenning of Basement membrane
deposits are : Subepithelial deposits
as it's above the membrane & below the podocyte
∴ called as Epimembrane deposits
B/w each deposits there is one normal B.M. ∴
called as SPIKE & DOME APPEARANCE.
$\underbrace{\text{SPIKE}}_{\text{BM}}$ & $\underbrace{\text{DOME}}_{\text{Immune complex}}$

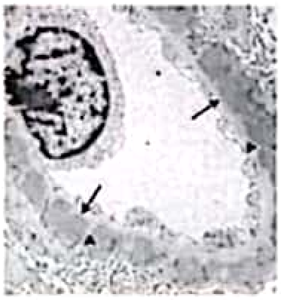
Size of DOME ∝ Severity of MGN
DOME ↳ PLA_2® Ag

Spike & Dome appearance can be easily visualised with Silver stain / PAS Stain on LM



MEMBRANOUS GLOMERULONEPHRITIS.
It reveals multiple "spikes" diffusely distributed in the glomerular capillary basement membranes. The appearance is produced by the deposition of silver-positive basement membrane material around silver-negative immune complex deposits.

- Clinical Features :
  - Adults
  - MCC of Neph-Syn in elderly
  - MC presentation :
    Massive proteinuria
    [NON-SELECTIVE]
  - may have HTⁿ & Hematuria



MEMBRANOUS GLOMERULONEPHRITIS showing "Spike and dome appearance" containing deposits of electron-dense immune complexes (arrows) forming "dome", with intervening delicate projections of basement membrane material (arrowheads) forming "spike".

Focal Segmental Glomerulo Sclerosis : FSGS

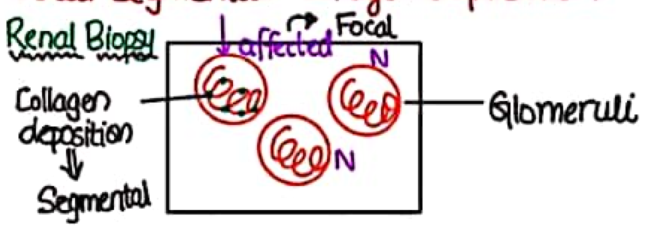
- MCC of Nephrotic syndrome in adults
- Etiology :

Primary
(Unknown)

Hereditary
i. NPHS- 1/2
ii. α-actinin-4
iii. TRP-C-6
↑ FSGS risk & ↑ Renal Failure
is a/w APOL-1 gene
(Apolipoprotein L-1)
on Chromosome 22

Secondary
- can be d/t
  i) infection : HIV : FSGS (MC), MGN, MPGN } can be seen
  ii) Heroine abuse
  iii) Morbid obesity
  iv) Scarring (= ↑ collagen deposition)
    ↳ d/t a) Reflux Nephropathy
    b) HTN Nephropathy
    c) Renal ablation
    d SCA / IG-A Nephropathy

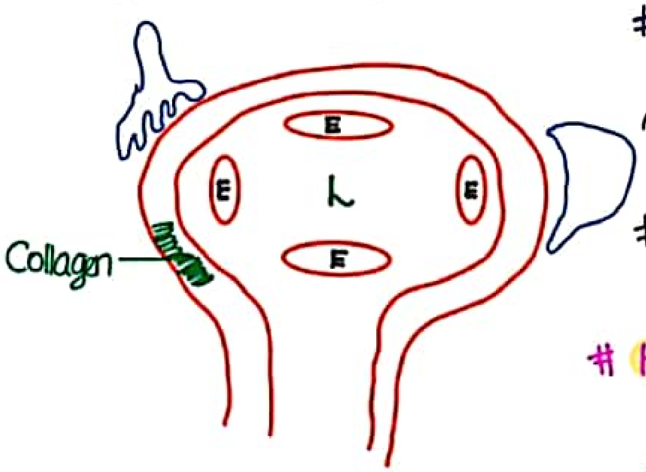
- Light Microscope : Focal Segmental Collagen deposition



Histological Sub types

① Glomerular tip variant : BEST PROGNOSIS
② Collapsing variant : WORST PROGNOSIS
③ Perihilar variant
④ Cellular variant
⑤ Not otherwise Specified

- On IF : IgM + C_3 deposits on sclerotic area
- On EM :



Visceral Epi. Damage : HALLMARK

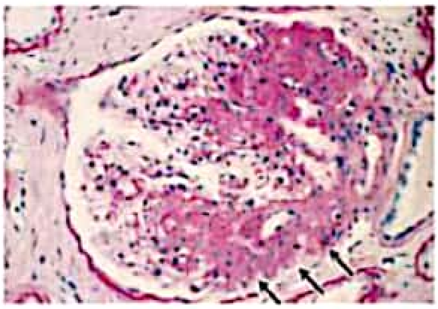
└ HYPERTROPHY
DISRUPTION

↓

diffuse effasement of foot process

HIV - Associated Nephropathy /
FSGS In HIV
⇓
There will be complete collapse of Glomerular cappillaries
⇓
Collapsing variant of FSGS : WORST PROGNOSIS

On EM : TubuloReticular inclusions within Endothelial cells
These are ER d/t IFN t/t.



FOCAL SEGMENTAL GLOMERULOSCLE-ROSIS

Periodic acid-Schiff (PAS) staining shows perihilar areas of segmental sclerosis and adjacent adhesions to the Bowman capsule (arrows).

Membrano Proliferative Glomerulo Nephritis

- These are immune complex mediated disorder
↓
a/w PERSISTENT HYPOCOMPLEMENTEMIA d/t Nephritic Factor Ab

1. Nephritic Factor of Classical Pathway - C_4NeF
2. Nephritic Factor of Alternative Pathway - C_3NeF
3. Nephritic Factor of Terminal pathway - NF_T

- TYPES OF MPGN

MPGN-1

- * MC type of MPGN
- * Pathology :
  activation of both classical & alternative complement pathway
- * a/w C_4 NeF
- * a/w
  - i) A.I dis : SLE
  - ii) Inf : Hep B/E, HIV
  - iii) Mixed Cryoglobulinemia

MPGN-2

- * 2^{nd} most common
- * C_3NeF
  ↓
  Activation of alternative complex pathway
  ↓
  Immune complex form.
  # IC : C_3 & Properdin
  & no Ig
  ∴ aka C_3 Glomerulopathy
- * a/w Partial Lipodystrophy

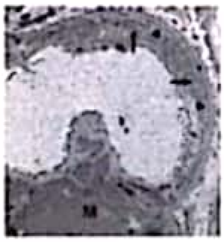
MPGN-3

- * Rare
- * a/w Complement Factor deficiency
- * NF_T ab

- Light Microscopy : Same for all

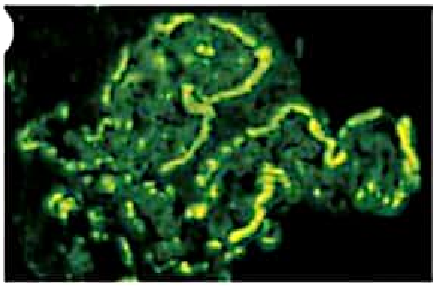
- * HYPERCELLULARITY
- * DOUBLE CONTOUR APPEARANCE / Duplication of BM / Tram-track appearance/Splitting of BM
- * Mesangial cell proliferation
  ↓
  Mesangial cell inter position i.e b/w E & BM
  ↓
  ∴ also Tram track appearance

	MPGN-1	MPGN-2	MPGN-3
- On Electron microscopy :	↓ Subendothelial deposition	↓ Intramembranous deposits because it's very thick aka Dense-deposit disease	↓ all types of deposits
- On IF	↓ IgG, M, C_3 Granular IF pattern	↓ C_3 & Properdin : dense Band Pattern of IF pattern	↓ Ig + C_3 Granular IF



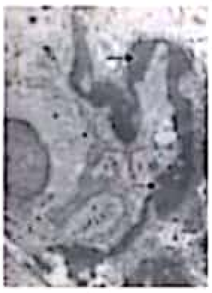
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS TYPE I (EM)

Showing characteristic discrete electron-dense immune complex deposits along the subendothelial aspect (arrowheads) of the original glomerular basement membrane and between duplicated basement membranes (arrows). Large, confluent electron-dense deposits are also identified within mesangial regions (M)



C3 GLOMERULOPATHY (DENSE DEPOSIT DISEASE OR MPGN II)

An immunofluorescence microscopy showing bands of capillary wall staining and coarsely granular mesangial staining for C3.



C3 GLOMERULOPATHY (DENSE DEPOSIT DISEASE OR MPGN II) (EM)

An electron microscopy shows thickening of the basement membrane with intramembranous dense deposits (arrows)

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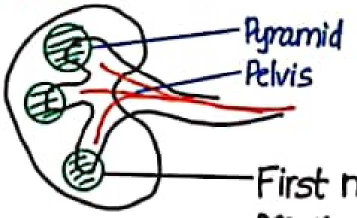
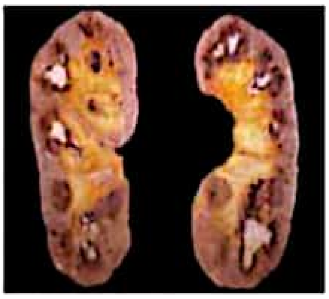
DIABETIC NEPHROPATHY

- Most important factor for development of this order is duration of disease
  TYPE -1 DM = Risk is 30-40%. for 20 yrs
  TYPE -2 DM = Risk is 20%.
- Pathogenesis : Insulin-deficiency
  ↓
  HYPERGLYCEMIA
  ↓
  Non-enzymatic glycation of proteins of B.M
  ↓
  - ↑ Glomerular capillary pressure
  - Glomerular Hypertrophy
  - ↑ GFR
- Lab findings : Earliest ⟶ ↑ GFR ≫ Microalbuminuria
- Gross finding :



Microangiopathy
↓
Ischaemia
↓
Necrosis

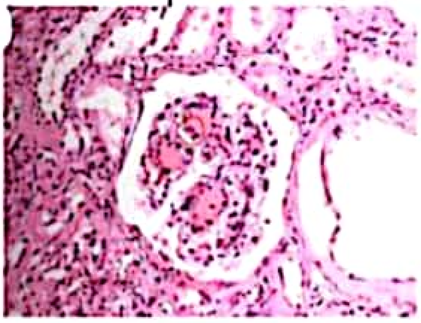
Called as Papillary Necrosis
↳ MC a/w DM
Other reason :
i. Analgesic (NSAIDS) Abuse
ii. SCA
iii. Chronic alcoholism



PAPILLARY NECROSIS

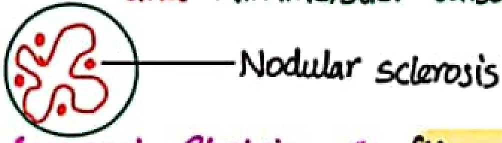
Showing well preserved renal cortex and papilla (tip of the pyramid) is replaced by yellow necrosis. (Renal papillary necrosis is seen as the pale white necrotic areas involving some or all renal papillae. Each renal papillae can be either partially or completely involved.)

- Microscopic Examination :
  i. Earliest finding : Capillary BM thickening
  ii. MC presentation : Diffuse glomerulosclerosis
  iii. Most specific : Nodular glomerulosclerosis
  aka Intercapillary Glomerulosclerosis
  aka Kimmelstiel wilson disease

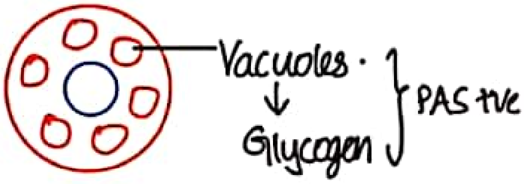


NODULAR GLOMERULOSCLEROSIS (= KIMMELSTIEL-WILSON DISEASE)

Ovoid, spherical, and nodular hyaline masses in peripheral of glomeruli obliterating glomerular tuft.



iv. Armaani-Ebstein cells (Uncontrolled DM)
⇒ PCT Epithelial cells



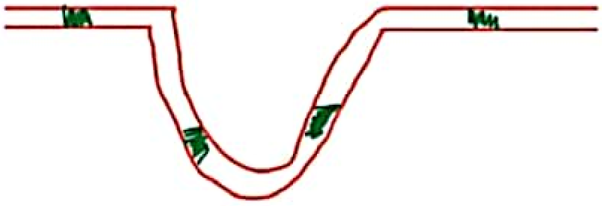
TUBULAR & INTERSTIAL DISORDERS

Acute Tubular Necrosis (ATN)

- due to i) Ischaemia : MCC of ATN
  ii) Toxins : Pb, Hg, Ethylene glycol.

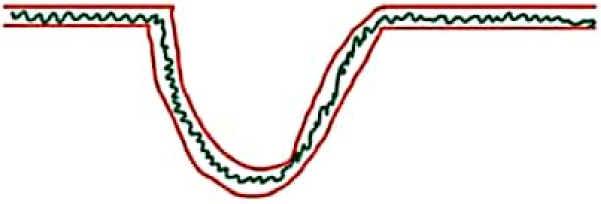
- MC site for ATN : Proximal Convoluted Tubules

ISCHAEMIA



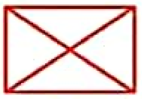
- ✱ patchy necrosis
- ✱ poorer prognosis

TOXINS



- ✱ Continous necrosis
- ✱ Prognosis : Better

- Urinary Examination : • Muddy casts ⊕
  • In Ethylene Glycol poisoning ⟹



Calcium oxalate crystal
(MC urinary crystal)

Tubulo interstial Nephritis

- aka Salt loosing nephritis
  - ✱ a) Loss of salt
    b) Metabolic acidosis
  - ✱ Aristolochic Nephropathy
    - Tubulo interstial disorder caused by Herbal medicine known as Aristolochic acid
      ↓
      form Free radical
      ↓
      damage of tubules & interstium
    - Risk for carcinoma transformation in Kidney & Urinary tract.

Pyelo Nephritis

- Infection of Tubules, pelvis & interstitium
- MCC is E. Coli Infection
- Routes of infection :

Ascending
- ✱ MCC of Pyelonephritis
- ✱ d/t reflux from Lower U.T to Kidney

Hematogenous

- PYELONEPHRITIS

Acute
- ✱ neutrophilic infiltarate → Suppurative inflammation

Chronic
- ✱ d/t chronic reflux nephropathy or reflux nephropathy

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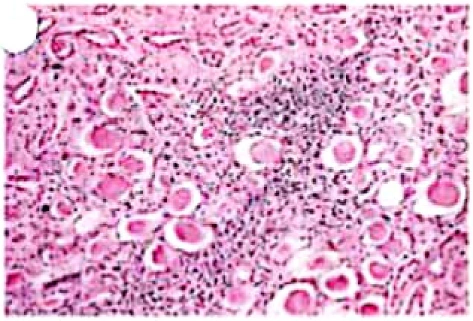
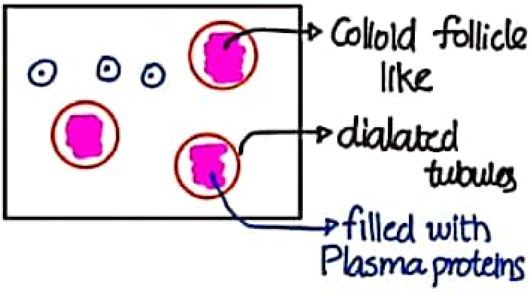


CHRONIC PYELONEPHRITIS (LM)

A light micrograph showing tubular dilation and atrophy. Many tubules contain eosinophilic hyaline casts resembling the colloid of thyroid follicles (so-called Thyroidization). The interstitium is scarred and contains a chronic inflammatory cell infiltrate.

* Lympho-plasmacytic Infiltarate
* Microscopic Examination

THYROIDISATION OF TUBULES

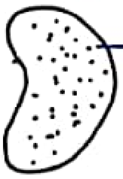


- Urine Examination : PYURIA (WBC in urine)
  WBC Casts

VASCULAR LESIONS

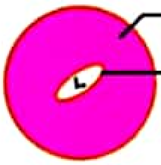
Benign Nephro sclerosis

- Gross :

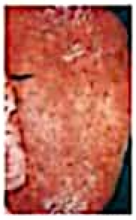


- B/L Symmetrical contracted kidney
- fine & Leathery Granularity on outer surface

- Microscopic :



Pink Hyaline
i) Narrowed Lumen
called as Hyaline arteriolosclerosis

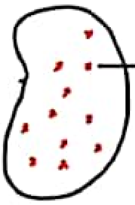


BENIGN NEPHROSCLEROSIS (GROSS APPEARANCE)

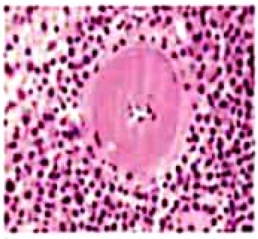
Showing cortical surface with fine and leathery granularity of the surface

Malignant Nephrosclerosis

- Gross :



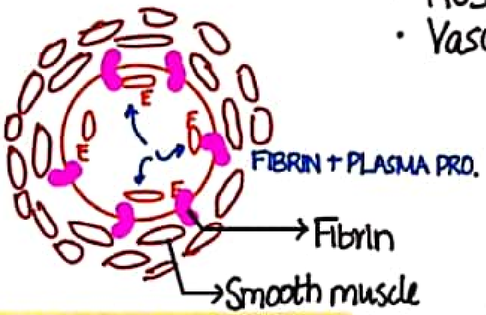
Pin point Hemorrhages d/t Rupture of arterioles & capillary
⇓
Flea - Beaten Appearance
↳ Causes : • HTN
• Infective endocarditis
• HUS
• Vasculitis (PAN)



BENIGN NEPHROSCLEROSIS (LM)

Hyaline arteriolosclerosis showing arterioles with hyaline deposition leading to marked thickening of the walls and luminal narrowing

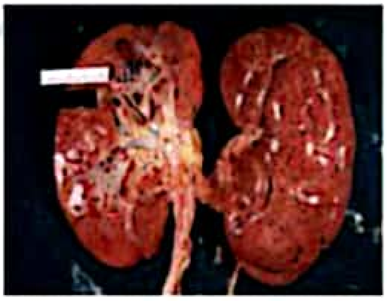
- Microscopy :



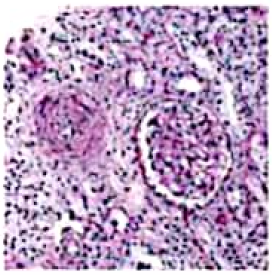
① HYPERPLASTIC ARTERIOLO SCLEROSIS
② FIBRINOID NECROSIS
ONION SKIN/BULB APPEARANCE

Random Blood flow
↓ Ⓔ damage
↓ Fibrin & plasma proteins leaking outside
↓ deposition over smooth muscle

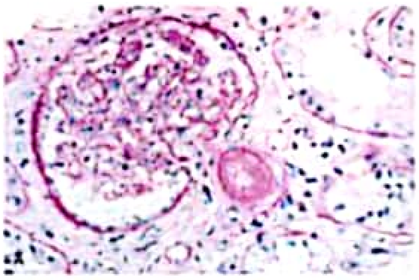
Random Blood flow → Hyperplasia of smooth muscle



MALIGNANT NEPHROSCLEROSIS (GROSS)
Numerous small petechial hemorrhages on the cortical surface giving a "flea-bitten" appearance to the kidneys.



MALIGNANT NEPHROSCLEROSIS (LM)
Thickening of the renal arteriolar wall associated with a hyperplastic arteriolosclerosis (hyperplastic arteriolitis). This arteriole has an "onion skin" appearance due to endothelial and muscular hyperplasia.



MALIGNANT NEPHROSCLEROSIS (LM)
Fibrinoid necrosis in the arteriole showing normal muscle layer of the media has been replaced by the fibrinoid material.

CYSTIC LESIONS

Autosomal Dominant Polycystic Kidney Disease

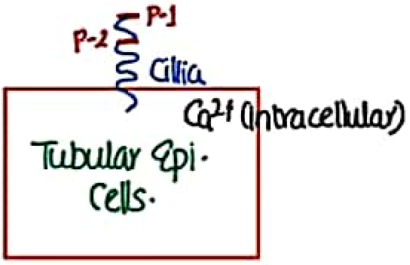
- Seen in Adults
- MC : Asymptomatic ∵ initially only few nephrons are affected.
  ↓
  CRF starts by the age of 40-60 yrs
  (Symptomatic)
- Etiopathogenesis :

Mutations in

PKD-1 (MC mutation) → Polycystin-1

PKD-2 → Polycystin-2

Function: control intracellular Ca^{2+} in response to fluid flow



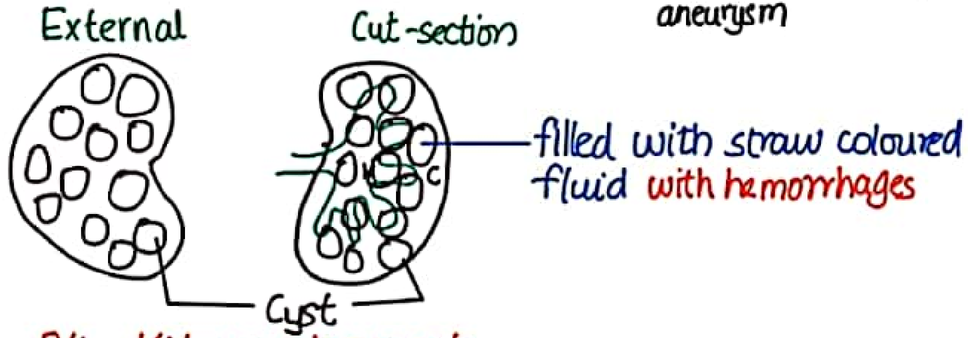
Mutations in → ↑ IC Ca^{2+}
↓
i. ↑ proliferation of cells
ii. ↑ apop of cell
iii. ↑ secretion from tubular cell
⇓
Tubular Cysts

- Clinical features :
  - MC : Asymptomatic
  - CRF @ 40-60 yrs
  - Symptoms : Hematuria
    Proteinuria
    Hypertension
  - MC Extrarenal manifestation of ADPKD :
    i. CYST in LIVER ≫ Colonic Diverticulum
    ↓
    ii. Spleen
    iii. Pancreas
    iv. Ovary
    v. Lung (Rarely)

Scanned with CamScanner

- Other extra renal manifestation
  - i. Colonic diverticula
  - ii. Berry's Anerysm
  - iii. Mitral Valve prolapse
  - iv. Extra renal cysts.
- MC cause of death : HTN & Coronary Heart disease
  - 2^{nd} most : Infection
  - 3^{rd} most : Rupture of Berry's aneurysm

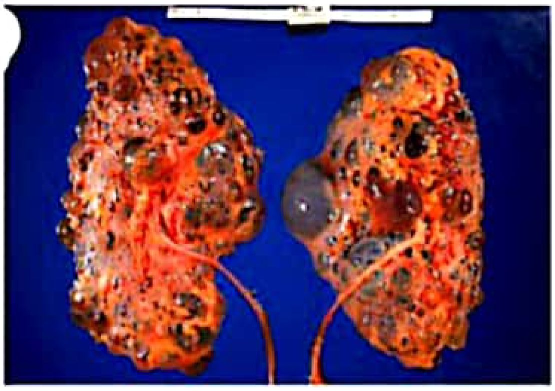
- Gross :



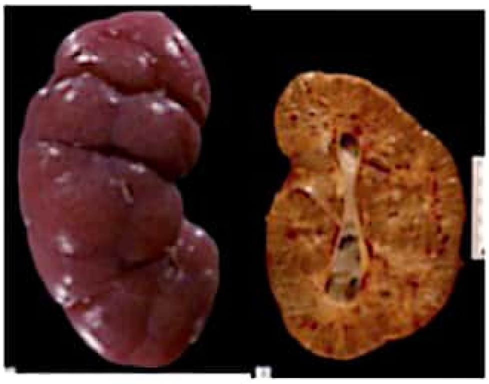
B/L Kidney enlargement

Autosomal Recessive Polycystic Kidney Disease

- Seen in pediatric age group (In First decade : death)
- Mutation in PKHD gene (Fibrocystin mutation) function & same pathogenesis
- MC Extra renal Manifestation : Congenital Hepatic Fibrosis
  Other " " : Hepatic cysts
- GROSS : External surface → Smooth i.e no cysts
  Cut section → Cylindrically dialated Collecting Duct involving both cortex & medulla Radially arranged
- Most common cause of death : Renal Failure



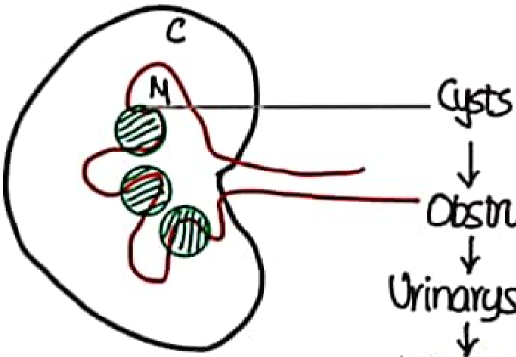
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE.
are enlarged and studded with multiple fluid-filled structures. Renal parenchyma is almost entirely replaced by cysts of varying size.



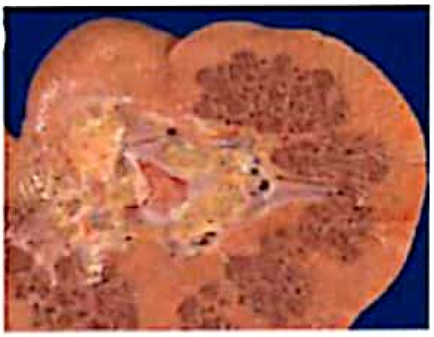
AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE.
The dilated collecting ducts (Both cortical and medullary) are arranged radially and the external surface is smooth.

Medullary Sponge Kidney Disease

- ✱ MC sporadic > Heriditary (AD)
- ✱ Adults



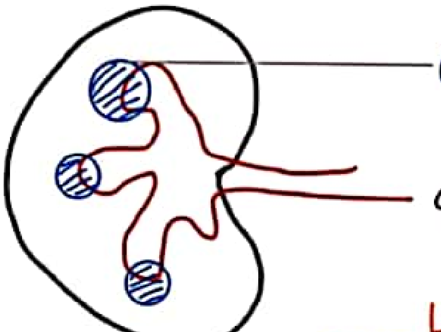
Cysts
↓
Obstruction
↓
Urinarystasis
↓
Infection
↓
Nephrocalcinosis



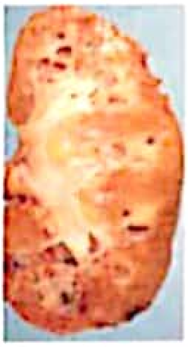
MEDULLARY SPONGE KIDNEY
Showing cysts involving the inner medullary and papillary regions in this kidney with normal cortex.

Medullary Cystic disease of Kidney

- ✱ Autosomal Dominant
- ✱ Adults



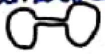
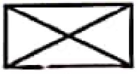
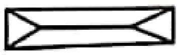
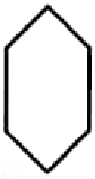
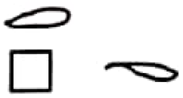
Cortico-medullary Cysts
↓
damage tubules & interstium
↓
Loose of Salt
Salt loosing Nephritis



MEDULLARY CYSTIC DISEASE
Cut section showing cysts at the corticomedullary junction and in the medulla.

RENAL STONES (= Nephrolithiasis)

- Males > Females ; 20-40 yrs
- Pre-disposing Factors :
  - i. Altered Urinary pH (Acidic/alkaline)
  - ii. Decreased urinary volume
  - iii. Absence of stone inhibitors
    Eg: Citrate pyrophosphate
    Osteopontin
- Stones /Calculi

CALCIUM OXALATE	STRUVITE	CYSTINE STONE	URIC ACID
• MC Stone • Seen in – Nephrolithiasis – Etrylene glycol poisoning • 2 types Monohydrate < Dihydrate (MC) Dumbell Shape  Envelope shaped 	(Tripple phosphate) (Mg - Ammonium Phosphate) • Seen in i. UTI (by Urea splitting bacteria) ii. Laxative abuse Prism shaped / Coffin-lid appe. 	 Hexagonal • Seen in Cystinuria	 Random shape & size • Seen in ↑ uricacid i. Gout ii. Tumorlysis syndrome

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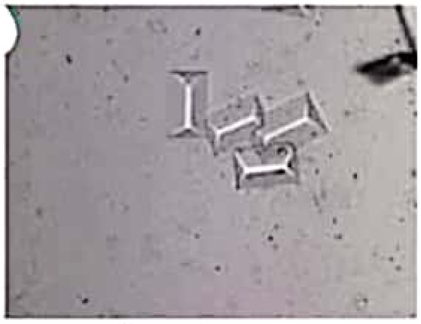
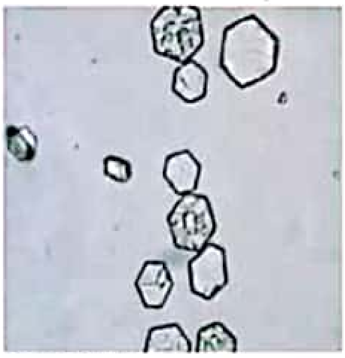
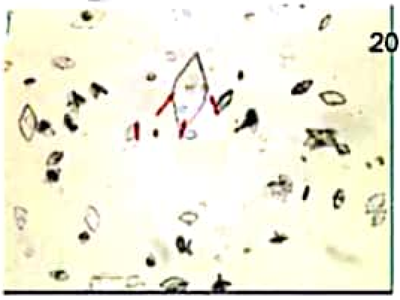


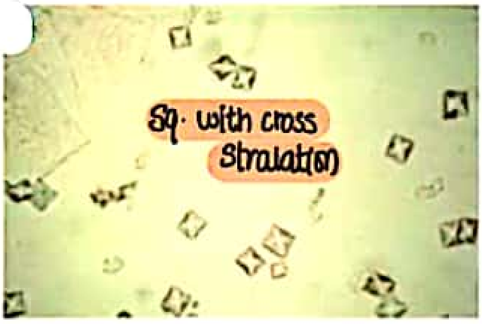
STRUVITE CRYSTALS (MAGNESIUM AMMONIUM PHOSPHATE, TRIPLE PHOSPHATE)
Three-dimensional prism-like crystals ("coffin lids")
Seen in UTIs caused by urea-splitting bacteria.



CYSTINE CRYSTALS
hexagonal shape with irregular sides.
Seen in cystinuria

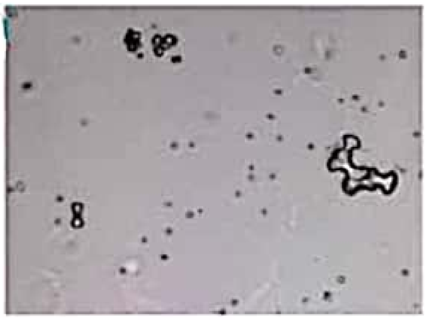


URIC ACID CRYSTALS
Usually lozenges but varying shape, yellow-tinged.
Seen in Acute uric acid nephropathy as part of tumor lysis syndrome.



Sq. with cross Straiation

CALCIUM OXALATE DIHYDRATE
small crystals that are square with cross-striations, resembling an "envelope".
Seen in High dietary oxalate ingestion, Ethylene glycol poisoning, Nephrolithiasis.



CALCIUM OXALATE MONOHYDRATE
crystals vary in size and may have a spindle, oval, or dumbbell shape.
Seen in Urolithiasis, Hypercalciuric or hyperoxaluric disorders,
Ethylene glycol poisoning

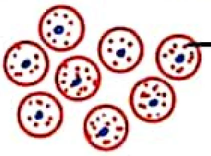
RENAL CELL TUMORS

BENIGN
i. Oncocytoma
ii Angiomyolipoma

MALIGNANT
i. Renal Cell carcinoma
& their histological subtypes

Oncocytoma

- Gross : Tan or Mahagony Brown colour
- M/E :

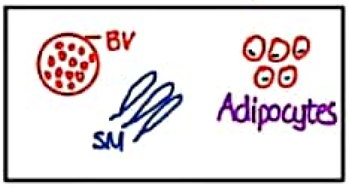


Hyper-eosinophilic granular cyto. [d/t Mitochondria]
⇓
ONCOCYTES

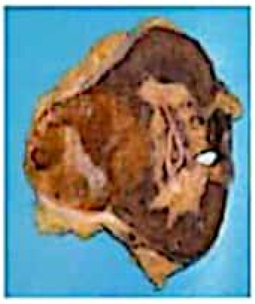
Sheets of tumor cell

Angiomyolipoma

- Hemartomatous lesion
↓
Blood vessels + Smooth muscles + Fatty tissue : M/E

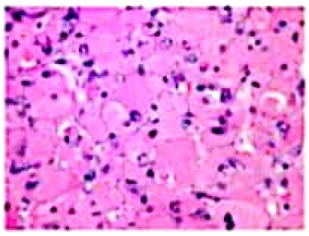


- associated with Tuberous Sclerosis



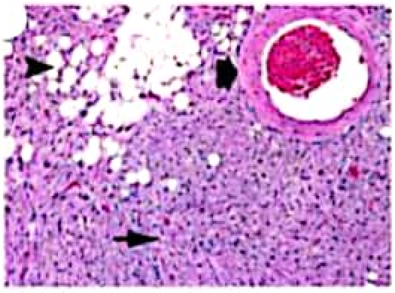
RENAL ONCOCYTOMA

Gross is showing "mahogany brown tissue with central stellate scar".



RENAL ONCOCYTOMA HISTOLOGY

Cells arranged in small nests.
Cytoplasm is finely granular and very eosinophilic.
Nuclei are round with inconspicuous nucleoli (may have occasional bizarre or "degenerative-type" nuclei; absent or rare mitosis.



RENAL ANGIOMYOLIPOMA

As the name implies, angiomyolipoma consists of a variable mixture of adipose tissue (arrowhead), smooth muscle bundles (lower arrow), and blood vessels (big arrow).

Renal Cell Carcinoma

- MC cancer in adults
- 40 - 60 yrs ; M>F (as Smoking is the strongest Factor)
- aka Grawitz Tumor / Hypernephroma
- Etiology : i. Smoking
  - ii. Obesity
  - iii. Hypertension
  - iv. ↑ estrogen exposure
  - v. asbetosis
- Clinical Features : i. Hematuria (MC presentation)
  - ii. Palpable abdominal mass
  - iii. Pain
  - } Triad
- MC they are SPORADIC > HEREDITARY
  - SPORADIC (90-95%) ↓ Unilateral (MC)
  - HEREDITARY (5-10%) ↓ Bilateral

Hereditary RCC - Bilateral

i. Von-hippel-Lindau syndrome
d/t VHL gene mutation } Chromosome 3p

Components
- i. M. Charachteristic ⇒ Cerebellar hemangioblastoma
- ii. Retinal angiomas
- iii. B/L Renal Cell carcinoma ⇒ MC : Clear cell RCC

ii. Heriditary Leiomyomatosis with Papillary RCC
- AD condition
- caused by FH Gene mutation (Chr. 1q)
  - ↳ Fumarate Hydratase
- Multiple cutaneous Leiomyoma with B/L Papillary RCC
  - ↳ More aggressive & Poor prognosis

iii. Birt-Hogg Dube Syndrome
- AD
- a/w BHD gene } MC a/w Chromophobe type RCC
  - FH gene ↳ a/w i) Chromophobe ii) Papillary RCC

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* Epithelial Tumors : MC adenocarcinoma

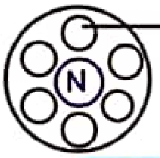
# RCC follow Hematogenous / Angioinvasive spread
↓
MC a/w Papillary RCC

# Paraneoplastic syndrome :
- MC : ↑ESR >>> ↑Ca^{2+}
- Hypertension
- Secondary polycythemia
- Secondary Amyloidosis (AA Type)

# MC Site for metastases RCC : LUNG.

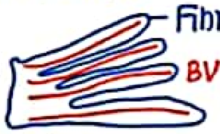
Histological Classification of RCC

i) Clear Cell RCC
- MC Type of RCC
- Origin : PCT Epithelium
- M/E : Tu Cells



Vacuolated Cytoplasm
↓
Lipid & Glycogen both

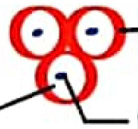
- Cytogenetic : i) MC change : Chr. 3p deletion
  - ii) t (3:6)
  - iii) t (3:8)
  - iv) gain of chr 5q

ii) Papillary RCC
- (=Chromophilic)
- PCT > DCT : Origin
- 

FIBROVASCULAR CORE : Seen in True papilla

- ∴ MC a/w Hematogenous spread
- a/w Dialysis a/w Cystic lesions of Kidney (MC)
- Molecular cytogenetics :
  - i) Trisomy 7 . a/w Hereditary Papillary RCC
  - ii) Trisomy 16
  - iii) Trisomy 17
  - iv) MET Proto-oncogene mutation

iii) Chromophobic RCC
- BEST PROGNOSIS
- Origin : CT
- Microscopy : 'Plant cell like'

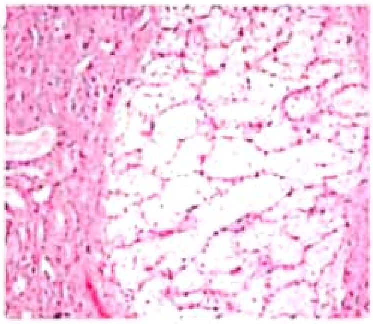


# Positive for Hale's Colloidal Iron
- Molecular Cytogenetics:
  - i) Loss of multiple chromosome Eg: 1,2,6,9 etc
  - ii) HYPODIPLOIDY

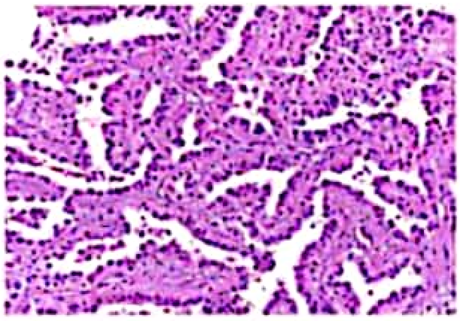
iv) Bellini duct Ca
- WORST PROGNOSIS
- Origin : CT
- a/w multiple chr. losses
- a/w Fibrous stroma (DESMOPLASIA)

v) RCC a/w XP11/TFE-3
- a/w translocations involving XP11
  ↓
  production of TF-E3
- mixture of Clear cell tumor on papillary projection.
- Molecular cytogenetics :
  - t(X:1)
  - t(X:17)

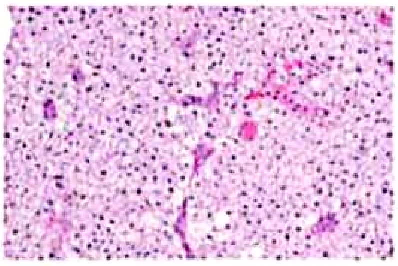
Medullary RCC : a/w Sickle Cell Anemia



CLEAR CELL TYPE RENAL CELL CARCINOMA' showing tumor cells with clear cytoplasm, typically arranged in nests.



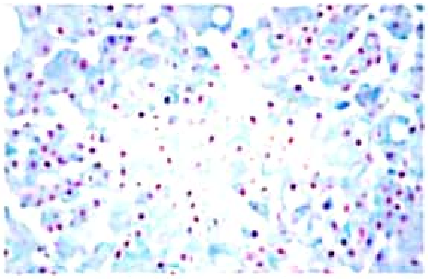
PAPILLARY RENAL CELL CARCINOMA It is composed of several tubulo-papillary strucures. There is nuclear enlargement and hyperchromasia, prominent nucleoli and more abundant eosinophilic cytoplasm.



CHROMOPHOBE RCC Chromophobe RCC with admixture of classic (chromophobic) and eosinophilic cells. Characteristic features include perinuclear halos, nuclear "raisins", and distinct cytoplasmic borders and cytoplasm condenses around the edges, giving the appearance of thick prominent cell borders ("plant cell-like")

WILM'S TUMOR :

- MC Renal Cell carcinoma in pediatric age group
- 2-5 yrs
- Usually sporadic & unilateral
  5-10% cases are hereditary & bilateral
- Associated with
  i) WAGR-Syndrome
    - d/t WT-1 gene mutation in chr. 11p
    - a/w Wilm's Tumor
      Anirldia
      Genital Malformation
      Mental Retradation
    - 33% Risk for Wilm's Tumor

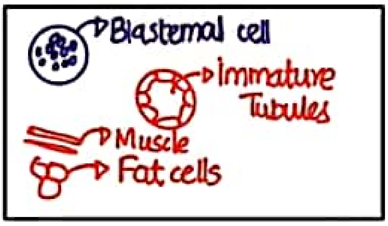


HALE'S COLLOIDAL IRON STAIN (SPECIAL STAINING) Hale's colloidal iron stain is positive (blue) i.e. deep blue granular cytoplasmic positivity in the cytoplasm of Chromophobe RCC.

  ii) Denys-Drash Syndrome
    - Maximum risk for Wilm's Tumor (>90%)
    - a/w :
      i. Gonadal dysgenesis
         (= Male pseudohermaphroditism)
      ii. Nephropathy leading to RF

  iii) Beckwiedth Weidman Syndrome
    - a/w Chromosome 11p
      WT-2 gene
    - a/w Genomic imprinting
      (Uniparental disomy)
    - Components
      i. Hemi hypertrophy
      ii. Organomegaly
      iii. Adrenal cytomegaly

- Clinical Features :
  - MC : Abdominal mass
  - Least common : Hematuria
  - Fever, Hypertension
- Microscopic examination : Triphasic Tumor
  i) Blastemal cells
  ii) Epithelial component
  iii) Stromal Cell



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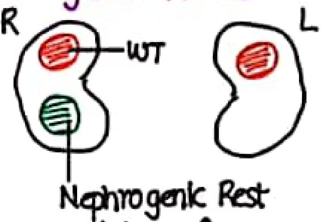
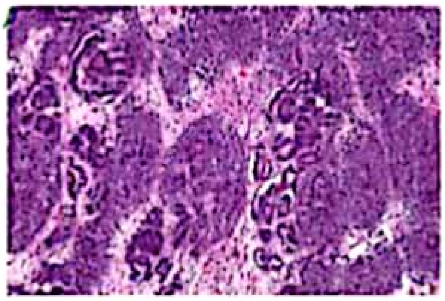
Nephrogenic Rests : These are precursor of WT in opposite Kidney



– It consists of Fibrous tissue enclosing immature tubules



WILMS TUMOUR
A) Malignant small round (blue) cells twice the size of resting lymphocyte (blastema component).
B) Tubular structures/rosettes (epithelial component).
C) Loose paucicellular stroma with spindle cells (stromal component)

MC Site for metastases : Lung tissue
Clear cell Sarcoma is a variant of WT
Here MC Site of Metastases : Bone
Prognostic factor
i) HISTOLOGICALLY
- Anaplasia : BEST MARKER
  More anaplasia, Poorer prognosis

ii) CYTOGENETICALLY
⇒ p53 mutation
⇒ Chr-1,16 loses

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CENTRAL NERVOUS SYSTEM

- Neurons
- Neuroglial Cell
  - Neuroectodermal origin
    ↓
    Glial Cells
    - Astrocytes
      - It's collagen counterpart (brain : No collagen)
      - fun: Wound healing & Repair
    - Oligo-dendrocytes
      - Required for myelin synthesis in CNS
      - ⇒ In PNS by Schwann Cells
    - Ependymal cell
      - Required for Ventricular lining
      - Once damaged they never regenerate
      - ∗ Ventricular damage causing ependymal damage
        ↓
        formation of subependymal granulation tissue by Astrocytes
  - Mesodermal Origin
    ↓
    Microglial Cells (Modified macrophage of brain)
    - # Modified microglial cell
      ↓
      fun: Ingest Myelin (lipid) aka Lipophages or Gitter cells or Hortega cells

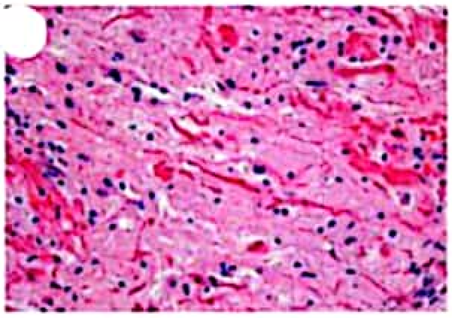
∗ Neuropathology of CNS Injury

1. Astrocyte responce to injury

(a) Rosenthal Fibers : Thick, eosinophilic, elongated, worm-like or cork-screw shaped bundles within astrocytes.

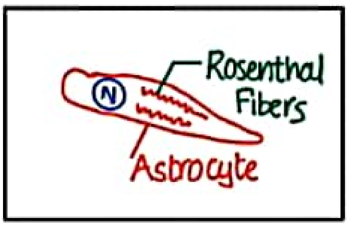
: Component :
mixtures of
Glial intermediate filament
+
Other cytoplasmic proteins (Eg: Heat shock proteins
Ubiquitin
α-β crystalline)

: a/w
i) Gliosis (Inflammation of brain)
ii) Tumors (Juvenile Pilocytic Astrocytoma)



ROSENTHAL FIBER

It is a thick, elongated, worm-like or "corkscrew" eosinophilic (pink) bundle composed of densely compacted glial intermediate filaments together with entrapped cytosolic proteins.



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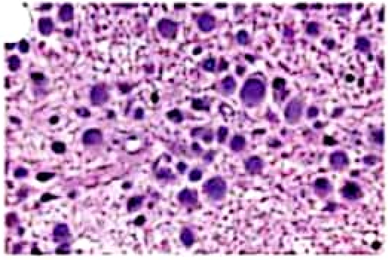
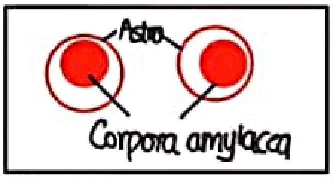
(b) Corpora Amylacea : consist of Polyglucosan Bodies (glucose polymers)



CORPORA AMYLACEA
Astrocytes with glucose polymer inclusion in the form of spherical inclusion bodies known as corpora amylacea. Seen in brain of advancing age.

: within astrocyte. Round-to oval cytoplasmic structure

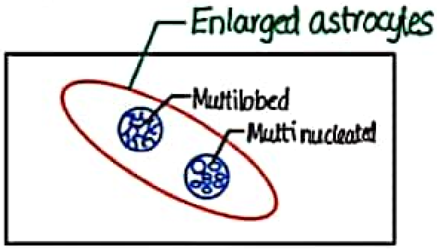


: Clinical significance:
a/w Degenerative changes in brain (ageing)

c) Alzheimer Cells (These are astrocytes) : NOT A/W ALZHEIMER'S DISEASE

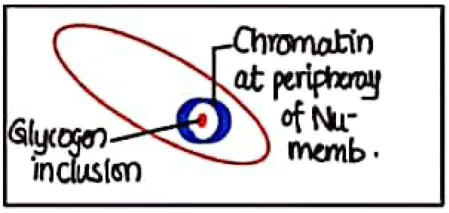
TYPE-1

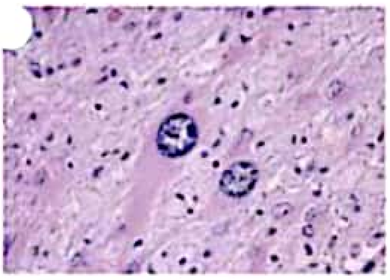
- seen in Progressive multifocal Leukoencephalophathy (PML)
- M/E :



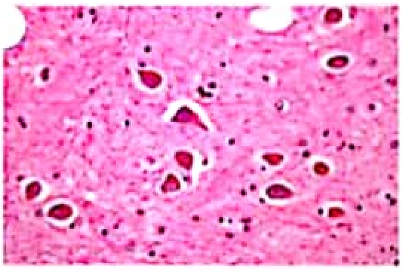
TYPE-2

- seen in Hyperammonemia d/t Liver cell failure
  Eg: Congenital defect in urea cycle
  Wilson's disease
- M/E :



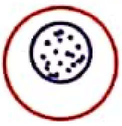


ALZHEIMER TYPE I ASTROCYTES
They have large, irregularly lobulated or multiple nuclei and clearly discernible eosinophilic cytoplasm.



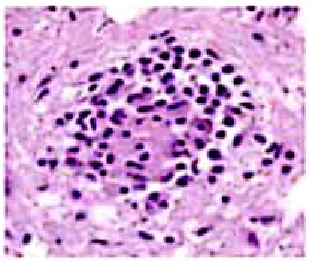
ALZHEIMER TYPE II ASTROCYTES
These are characterized by enlarged nuclei with thin chromatin and increased glycogen levels.

2. Oligodendroglial response to CNS injury
   - a/w DEMYELINATING DISORDER
     Eg. Subacute Sclerosis Pan Encephalitis by Measles infection
   - Oligodendroglial damage ⟶ i) Apoptosis
     ii) Viral inclusion
     Eg within nucleus: Ground glass oligodendro.



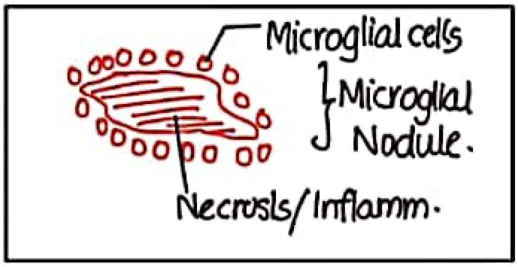
Seen in PML by JC polyoma Virus,

3. Microglial cells responce to CNS injury
   (a) Microglial Nodules : Collection of microglial cells around the necrosis / viral inflammation
   : Most charachteristic histological finding AIDS/HIV inf.

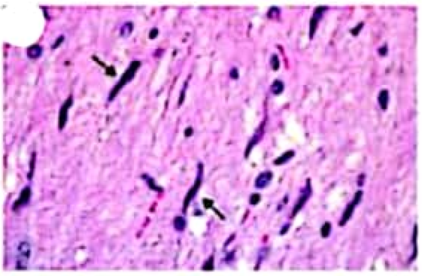


HIV ENCEPHALITIS
The cerebral cortex has perivascular inflammatory infiltrates containing microglial nodules consisting of prominent multinucleated giant cells are characteristic feature.

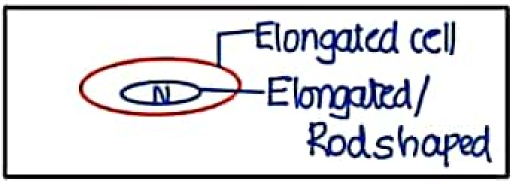
:



(b) In Neurosyphilis : Microglial modify to form Rods : Rod Cells



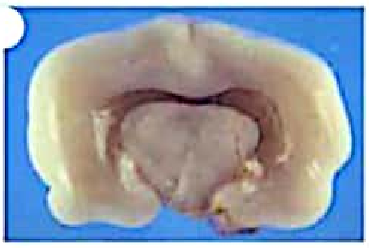
RODS OF NEUROSYPHILIS
Nuclei of microglia showing their elongated irregular nuclear morphology (arrows) is apparent.



FORE-BRAIN ANOMALIES

1. Holoprosencephaly

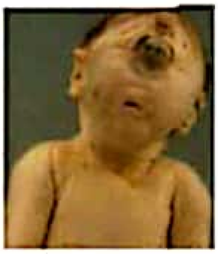
- Normal : 2 hemispheres (Right & Left)
  d/t Sonic HedgHog gene (SHH Gene)
  ↓
  It's a morphogenesis gene
  Function : i) Patterning of limbs
  ii) Patterning of midline structure like Brain, Spinal cord & Face
- SHH Gene mutation → No Right/ Left Hemisphere
  ↓
  Monoventricular cavity
- CYCLOPIA : Single Eye
  ill developed mouth & nose
- a/w Trisomy 13/ Patau Syndrome
  Maternal diabetes mellitus



HOLOPROSENCEPHALY
A coronal section of the brain showing forebrain of the embryo fails to develop into two cerebral hemispheres (holoprosencephaly) with monoventricular cavity

2. Lissencephaly /Agyria

- Etiology : i) Fetal alcohol syndrome
  ii) in-utero HIV-infection
  iii) LIS-1 gene mutation
- Normal Brain : Gyria & Sulcus present
  ↓ LIS Gene mutation
  FLAT BRAIN SURFACE/ Agyria



CYCLOPIA
Affected fetuses and neonates typically have severe facial defects like CYCLOPIA. Associated with trisomy 13 and maternal diabetes mellitus.

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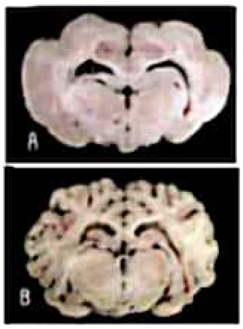
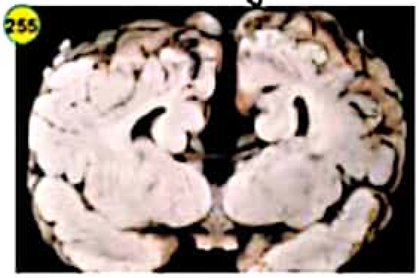
3. Neuronal Migration Disorder (NMD)



LISSENCEPHALY VS B) NORMAL BRAIN
Absence of cortical gyri in brain.

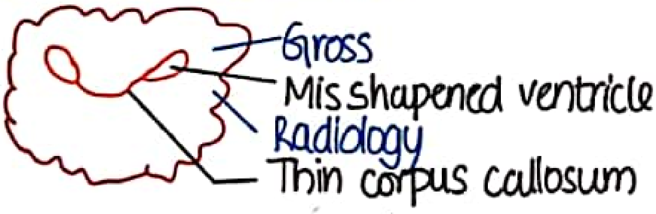
- Group of disorder where neuronal migration is deffective
- Normally Neuronal migration get completed by 12-16 weeks of IUT
- If it's incomplete by 12-16 weeks of IUT
  ↓
  NMD
- Etiology : i) DCX-1 gene mutation (Double Cortin Gene)
  ii) LIS-1 mutation
  iii) Filamin-A1 gene mutation
- Eg of NMD : i) Lissencephaly
  ii) Holoprosencephaly
  iii) Microgyria (Small numerous gyri)
  iv) Neuronal Heterotopia (Abn neuronal migration to abn sites)
  v) Agenesis of corpus callosum



AGENESIS OF THE CORPUS CALLOSUM
A section of the brain at the level of the thalamus reveals absence of the corpus callosum and "bat-wing" shape of the lateral ventricles.

AGENESIS OF THE CORPUS CALLOSUM
A section of the brain at the level of the thalamus reveals absence of the corpus callosum and "bat-wing" shape of the lateral ventricles.

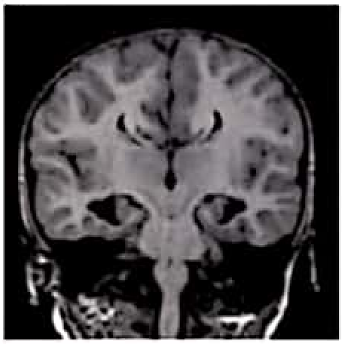
BAT-WING DEFORMATY
(d/t mishaped ventricle)
aka Racing Car Sign



POSTERIOR FOSSA - ANOMALY

1. Dandy-Walker malformation

- Cystic dilation of 4th ventricle
  ↓
  ∴ ↑ in post. fossa volume
  ↓
  HYDROCEPHALUS (d/t ↑ CSF)



BAT WING DEFORMITY
Bat wing deformity on CT scan.

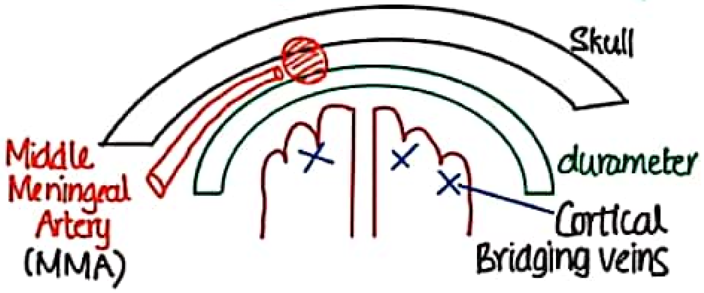
2. Chiari-malformation

- Cerebellar herniation
- 4 types i) TYPE-1 : Herniation of cerebellar tonsil
  ii) TYPE-2 : Herniation of cerebellar vermis
  iii) TYPE-3 : a/w occipital Encephalopathy
  iv) TYPE-4 : No cerebellar development
- HYDROCEPHALUS
- ↓ Post. Fossa Volume

Scanned with CamScanner

VASCULAR INJURY OF BRAIN

- EPIDURAL Hemorrhage
- Subdural Hemorrhage
- Intracerebral Hemorrhage
- Subarachinoid Hemorrhage



EPIDURAL Hemorrhage

* Rupture of MMA
↓
∴ arterial blood
* Emergency craniotomy required
# Lucid interval
Prolong & Charachteristic

Subdural Hemorrhage

* Rupture of cortical Bridging veins
∴ venous blood
# Lucid interval
Period of conciousness In b/w unconciousness

Intracerebral Hemorrhage

* MCC : Hypertension
* MC Type of Brain Hemorrhage

* MC Site: Middle Cerebral artery (Lenticulo striate branch)

* HTN
↓
Lipid & Hyalin mediated damage of BV (lipohyalinosis)
↓
Aneurysm (Charcot Boucher Aneurysm)
↓
Prone for rupture & Bleeding

*MC Site for HTN bleed : Basal ganglia (Puten : MC)

\#Rpt · HTN Bleeding
↓
HTN Encephalopathy
↓
Dementia (Binswanger ds)

Subarachinoid Hemorrhage

* MCC : Trauma
2nd MC : Berry's Aneurysm Rupture

* MCC of spontaneous Subarachinoid Heam: Berry's aneurysm
↓
- defective Tunica Media
- It involve circle of willis
- MC Site: Jn of Ant· cerebral artery with Ant· communicating branch
- Least common site: Vertebral artery
- It's a/w atherosclerosis (rarely)

CNS INFECTIONS

-Source of infection : i. Hematogenous : MC Route of spread
ii· Traumatic Direct spread
iii Axonal spread : Peripheral Nerve Eg : Rabies
Herpes zoster

CSF ANALYSIS

	Normal	Bacterial Meningitis =Pyogenic Meni.	Tubercular menin.	Viral meningitis
i. Gross appearance	: Clear & Colorless	Puslike or Yellowish	Cob Web coagulum (d/t Fibrin)	Clear & Colourless
ii. CSF Pressure	: 60-150 mmHg	↑	↑↑↑(max)	↑↑
iii. Cells Lymphocyte	: 0-5/μL	↑↑Neutrophil Count	↑↑↑ Lymphocyte (maximum)	↑ Lymphocyte
iv. Protein	: 15-40mg/dl	↑	↑	↑
v. Sugar/Glucose # $CSF_{Glucose} = \frac{2}{3} Serum_{Glucose}$	: 50-80 mg/dl	↓↓↓ (Severe)	↓ (mild)	Ⓝ
vi. Chloride	: 116-122mEq/L	↓ (mild)	↓↓↓ (Severe)	Ⓝ

Albumino-cytologic dissociation

- ↑ in protein is d/t ↑ cell count
- But in certain condition ↑ protein but cell count = Ⓝ

  Albumino cytologic dissociation
- a/w Guillian Barre Syndrome (Classically)

  Intracranial Neoplasia

  Late stage of polio infection

MENINGITIS

- MCC of meningitis : Viral > Bacteria

Viral ↓ MCC: Enterovirus ↓ MCC of aseptic meningitis

Bacteria ↓ MCC : Strep. pneumoniae

1. TB Meningitis

- Hematogenous-spread (=miliary TB)

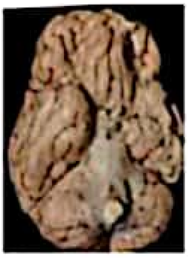
  ↓

  Cerebral cortex showing Granuloma known as RICH Focus
- MC presentation of TB meningitis : Diffuse meningo encephalitis

  meningo ↓ Meningeal inflam. encephalitis ↓ Brain parenchyma

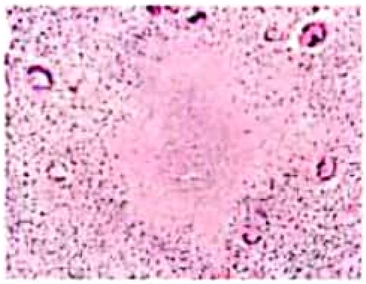
Scanned with CamScanner

- Most charachteristic presentation : Basal exudates on Gross & Radiological examination
- On Histopathological analysis :
  1. Caseating Granuloma



TUBERCULOUS MENINGITIS
Gross specimen of the brain showing a thick, gelatin-like basal exudate.

- Complications :
  - ✱ MC complication : Cerebral infarction
  - ✱ Exudates → Adhesive arachnoiditis
  - ✱ involve Cranial nerve → Palsy
  - ✱ Hydrocephalus (d/t blockade of CSF outflow)



TUBERCULOUS MENINGITIS
Showing caseating necrosis with numerous langhans giant cells

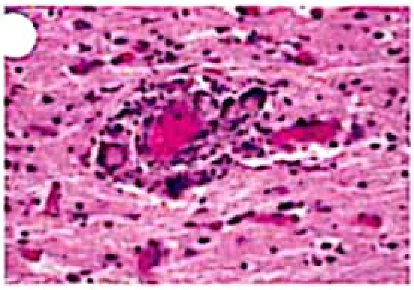
AIDS / HIV

✱ AIDS Dementia Complex
↓ features
i) Spare cortex
ii) Subcortical involvement

✱ Encephalitis
✱ Meningitis
✱ M/E :

- Most charachteristic : Microglial Nodules
- Multinucleated Giant cell
- Diffuse symmetrial demyelination of white matter
  (diffuse white matter necrosis)

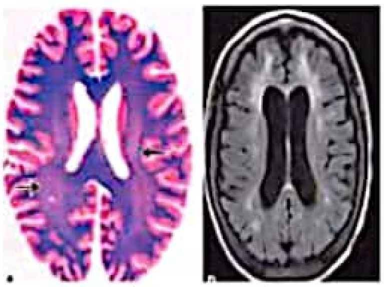
Demyelination seen in
i) HIV : Symmetrical
ii) PML Asymmetrical & Patchy



HIV ENCEPHALITIS
The cerebral cortex has perivascular inflammatory infiltrates containing microglial nodules consisting of prominent multinucleated giant cells are characteristic feature

- In spinal cord : Vacuolar myelopathy
- NEVER SEEN a) Viral inclusion
  b) No vasculitis

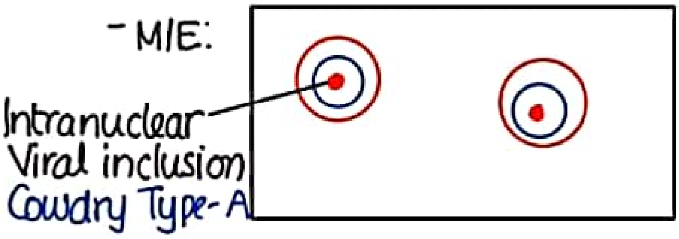
LUXOL FAST BLUE STAIN :
Used for myelin : Normal : Blue
Damaged : Pallor

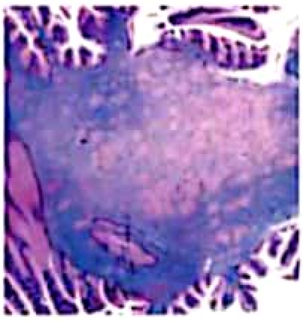


HIV ENCEPHALITIS (LUXOL FAST BLUE STAINING).
Whole brain section shows symmetric myelin pallor (arrows) caused by HIV-1

HERPES - SIMPLEX VIRUS - I

- Temporal & frontal lobe (MC)
- Classically presenting with
  - Alteration in mood, memory, behaviour
- M/E:



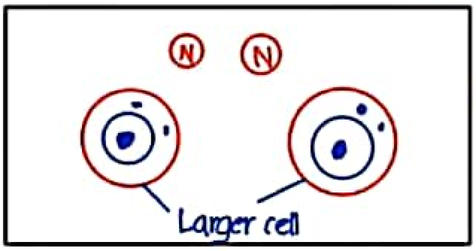


PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) (LUXOL FAST BLUE STAINING)
Demyelination caused by progressive multifocal leukoencephalopathy (PML) would be asymmetrical and patchy

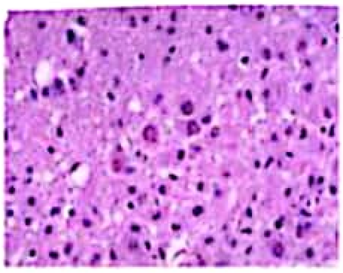
Scanned with CamScanner

CYTOMEGALOVIRUS INFECTION

- Usually in-uteroinfection → i. Microcephaly
  ii. Periventricular necrosis & calcification (Charachteristic finding)
- M/E :

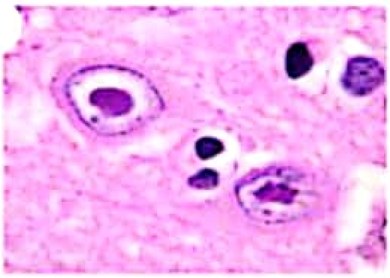


Viral inclusions
- Basophilic
- Intra nuclear
- Cytoplasmic



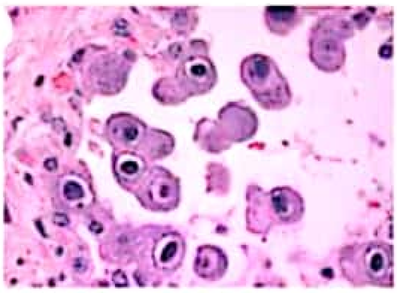
GROUND GLASS OLIGODENDROCYTES IN PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PML)

Showing Oligodendrocytes nuclei with intranuclear eosinophilic inclusions (Ground glass Oligodendrocytes).



COWDRY A INTRANUCLEAR INCLUSIONS

Cowdry A intranuclear inclusions in a case of herpes encephalitis



CYTOMEGALOVIRUS INFECTION

Enlarged cells with large intranuclear basophilic inclusions.

POLIOVIRUS INFECTION

- Aseptic meningitis
- Effect Lower motor neuron. ∴
  i. Muscle weakness
  ii. Atrophy
  iii. Fasciculations
  iv. Hyporeflexia
- MCC of death : Resp. muscle weakness
  ↓
  Respiratory Failure
- Usually involve Anterior horn of Spinal Cord.

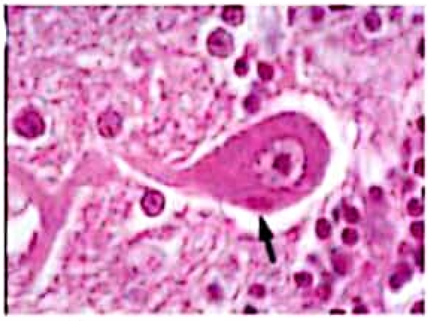
* Post polio Syndrome

- d/t Reactivation of polio virus (~25-30yrs)
- i. Weakness
  ii. Pain
  iii. Loss of muscle
  } in the same affected limb.

RABIES

# caused by Rabid-animal bite (Eg: Dog)

- Bite (Site) $\xrightarrow[\text{nerve}]{\text{peripheral}}$ CNS [axonal spread)
- I.P : 1-3 months
- Clinical Features : • Extra-ordinary CNS excitability
  • Hydrophobia
  • Flaccid paralysis
- Diagnosis : M/E : Negri bodies in
  i. Cerebellum (MC)
  ii. Brainstem
  iii. Hippocampus (MC in Dogs)

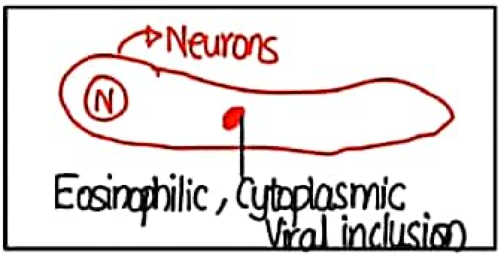


RABIES (NEGRI BODIES)

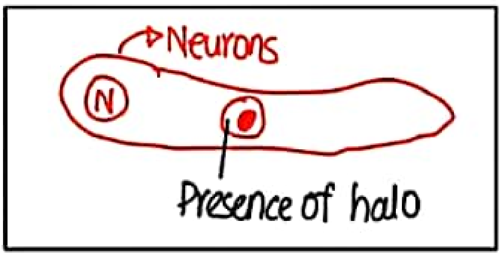
They are *eosinophilic*, sharply outlined, pathognomonic inclusion bodies (2–10 µm in diameter) found within cytoplasm of purkinje cells. Most commonly seen in *cerebellar purkinje neurons.*

Scanned with CamScanner

- M/E :

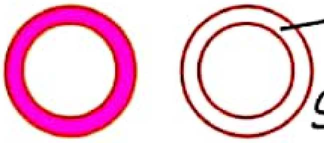


d/d : Lewy-Body in Parkinson disease



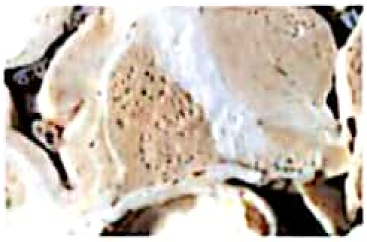
FUNGAL MENINGITIS

- MCC of fungal meningitis : Cryptococcus
- pt with ↓immunity (Eg: HIV infected)
  ↓
  Clinical signs & symptoms of Meningitis
- Gross : i) Numerous small cystic & necrotic area which are glistening (d/t Capsular polysaccharide)
  ii) giving rise to Soap Bubble abscess/appearance
  seen in i) Gross
  ii) M/E
  iii) Radiology
- M/E :

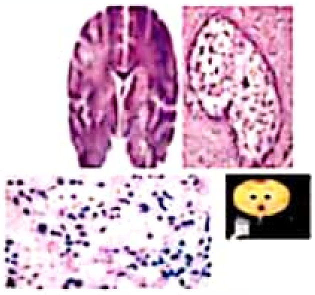


India Ink Stain (Negative stain)
background will be dark
organism : unstained.

- Virchow Robin Space in Brain :
  Maximum conc of cryptococcus.



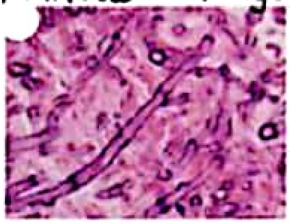
CRYPTOCOCCAL "SOAP BUBBLE" ABSCESSES
Encapsulated organisms occur in the Virchow-Robin space and in microabscesses within the parenchyma. The microbial capsule imparts a glistening clear appearance to these collections that has been likened to soap bubbles.



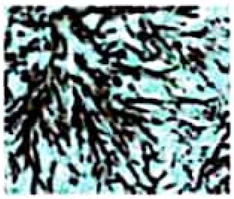
HEMATOXYLIN AND EOSIN STAIN
showing soap bubble cysts full of organism. Only center of the organism is visible thick gelatinous capsule remains unstained. Characteristic "soap-bubble" is the result of production of a thick capsule by the yeast.

ASPERGILLUS

- ⁎ Thin septate hyphae + acute angle branching
- ⁎ Anglo invasive fungal inf



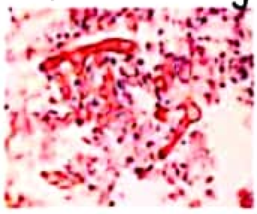
ASPERGILLUS
Thin septate hyphae with acute angle branching



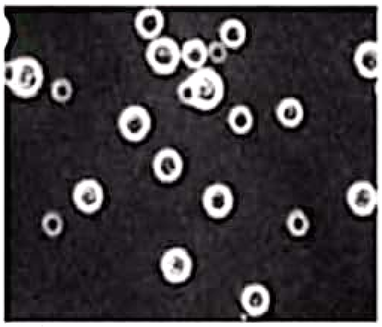
ASPERGILLUS: GOMORI METHENAMINE SILVER STAIN

MUCOR

- ⁎ aseptate broad & perpendicular branching
- ⁎ Anglo invasive fungal inf



MUCOR
Broad aseptate hyphae with perpendicular branching

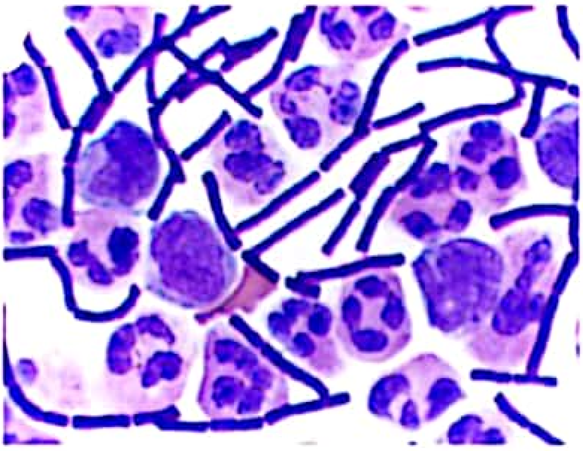


INDIA INK STAIN OF CRYPTOCOCCUS
showing capsule.

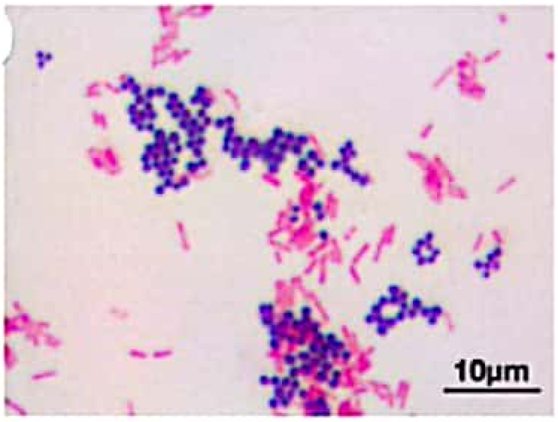
PROTOZOAL MENINGITIS

1. Naegleria

- necrotising meningoencephalitis
-



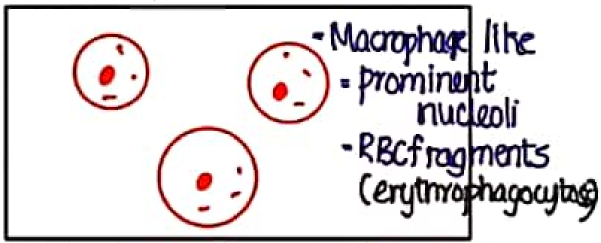
GRAM POSITIVE
Gram-positive cells staining purple



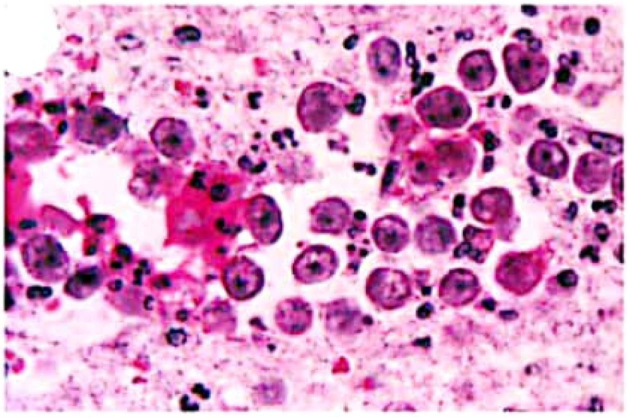
GRAM-NEGATIVE
Gram-negative cells staining pink

2. Acanthameba

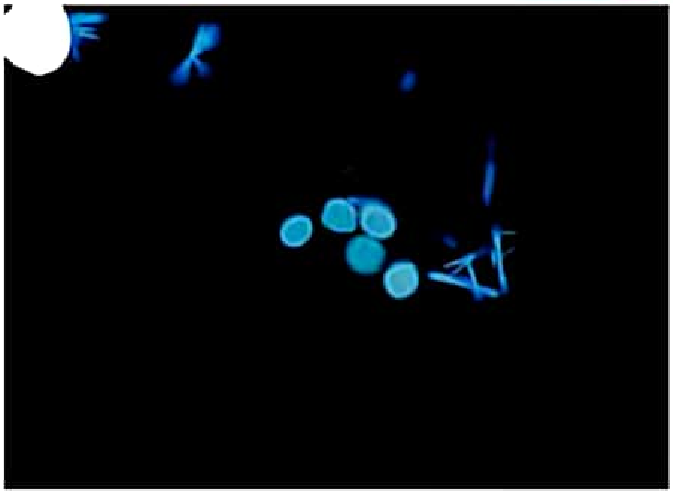
- Chronic granulomatous meningo encephalitis
- Immunocompromised patient
- M/E : Any Amoeba



IF Stain : Calcofluor White stain
↓
acanthameba cellwall : Optically greenish/Bluish white



ACANTHAMOEBA MENINGOENCEPHALITIS
Amebic organisms *resemble macrophages* but have much more *prominent nucleoli.*

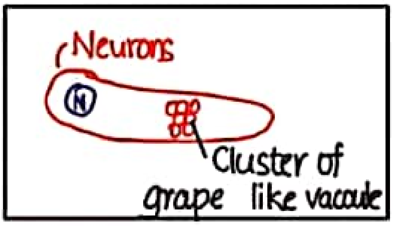


CALCOFLUOR WHITE
Used for detection of *cell wall of acanthamoeba* which will *appear optically greenish white.*

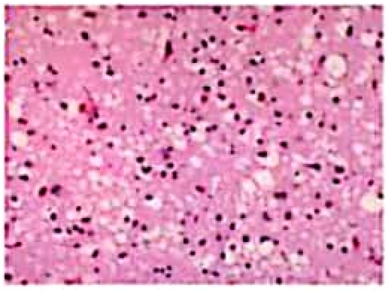
Scanned with CamScanner

PRION DISEASE

- Presenting with progressive dementia with longer I.P
- caused by infectious proteins (neither DNA nor RNA)
- can be familial, Sporadic (MC), Infectious
- Routes of infection : i. Iatrogenic (MCC) Eg: Neurosurgery, Corneal Transplantation
  ii. Infected brain ingestion
- Pathogenesis : Misfolding of protein
  Prion protein (PrP) : * Normally • α Helical
  • protease-sensitive
  * bcoz of inf. or contamination
  ↓
  Conformational change in structure
  ↓
  Abnormal PrP^{SC} (Scrape)
  ↳ • β-pleated sheets (+ve: Congo-red)
  • protease resistant
  ↓
  Damage of neuronal cytoplasm ← Excess of Abn PrP^{SC}
  ∴ Misfolding of protein
- Microscopic Examination :

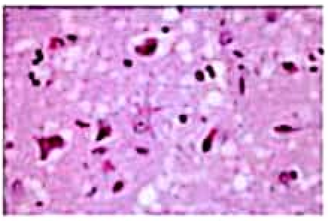


∴ called as Spongiform Neurons



PRION DISEASE WITH SPONGIFORM NEURONS
Showing formation of microscopic "holes" or vacuoles within the neuronal cells to give "spongiform appearence". Seen in all Prion diseases except fatal familial insomnia.

- Eg : i. Creutzfeldt Jacob Disease
  ii. Fatal familial insomnia : NO SPONGIFORM Neurons
  iii. Kuru
  iv. Scrapie
  v. Bovine spongiform Encephalopathy



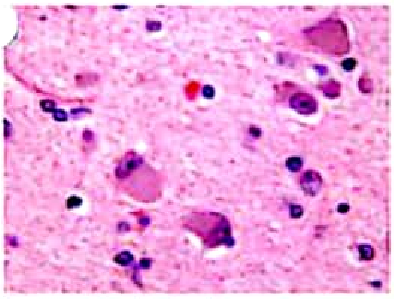
PRION DISEASE WITH SPONGIFORM NEURONS
Showing formation of microscopic "holes" or vacuoles within the neuronal cells to give "spongiform appearence". Seen in all Prion diseases except fatal familial insomnia

DEMYELINATING DISORDERS

- damage of myelin (oligodendrocyte)

1. MULTIPLE SCLEROSIS

- Autoimmune demyelinating disorders
- Bimodal age distribution ; F > M
- Etiology : 1. Autoimmune
  2. EBV inf
  3. IL-2, IL-7 Receptor polymorphism
- Pathogenesis : Both B Cells & T cell involved
  * Oligoclonal IgG band on CSF Analysis
  TH1 : ⊕ ↓IFN-γ Macrophage
  TH17 ↓ IL-17



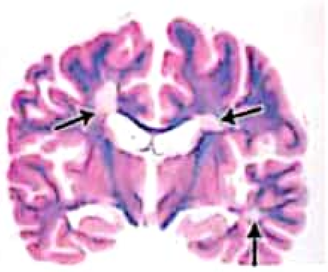
BALLOONED NEURONS
Ballooned neurons (Picks bodies) are seen in Lobar atrophy (Pick's disease).

TH1 ↓ IFN-γ ↓ activate macrophage ↓ DAMAGE

TH17 ↓ IL17 ↓ activation of Neutrophil, Monocytes | MYELIN

280

- M/E : LUXOL FAST BLUE STAIN
  ↓
  Peri-ventricular Pallor
  (d/t myelin damage)



MULTIPLE SCLEROSIS
This myelin-stained coronal whole brain section of the brain of a patient with long-standing multiple sclerosis shows many areas of myelin loss – plaques (arrows) – with characteristic periventricular demyelination especially prominent at the superior angles of the lateral ventricles.

- C/f : i) Optic neuritis (Unilateral)
  ↓
  impaired vision
  ii) Brain stem : Ataxia
  Nystagmus
  Internuclear ophthalmoplegia
  iii) Spinal cord : Motor neuron involvement Spasticity &
  Bladder dysfunction

2. DEVIC DISEASE [Neuromyelitis Optica)

- Similar to Multiple sclerosis : B/L Optic neuritis + Spinal cord pathology
- Antibodies against Aquaporin protein (genes)
  ↳ Required to maintain the foot process of astrocyte & Blood brain barrier intergrity

3. CENTRAL PONTINE MYELINOSIS

- MC Site : Basis pontis
- d/t rapid overcorrection of Na^+ by giving normal saline
  ↓
  Hypernatriemia
  ↓
  damage of myelin sheath
- Presentation : Spasticity

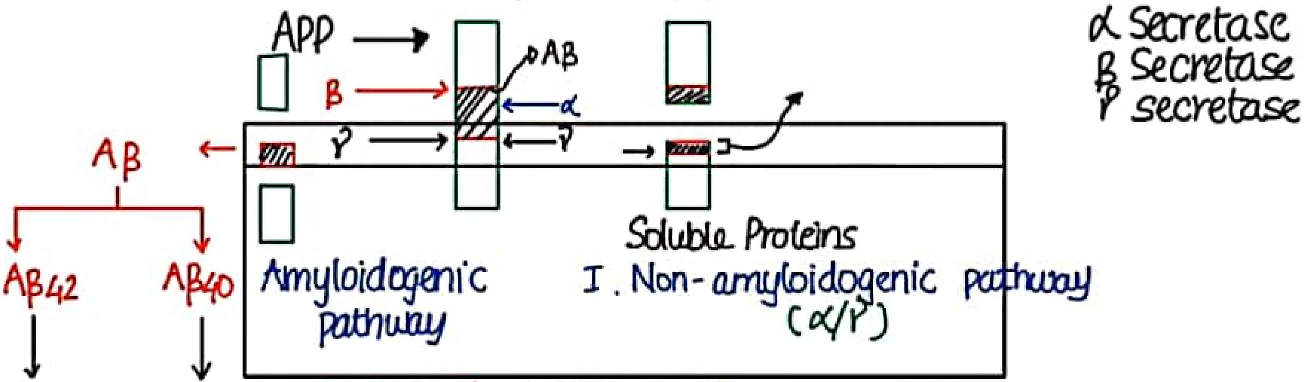
DEGENERATING DISEASE OF BRAIN

- Common : Grey matter neuronal damage by misfolding of proteins

1. ALZHEIMER DISEASE

- commonly in older age (>60yrs)
- MCC of Senile Dementia
- Etiopathogenesis : MC Sporadic, Some familial
  Genes : i. Amyloid Precursor Protein gene on Chromose 21 (APP Gene)
  ii. Presenil 1 : Chr. 14 iii. Presenil -2 : Chr. 1
  iv. Apolipoprotein E_4 (ApoE_4 : Chr 19 : Strongest heredial a/w AD

- APP Gene : * transmembrane protein
  * on chromose No: 21

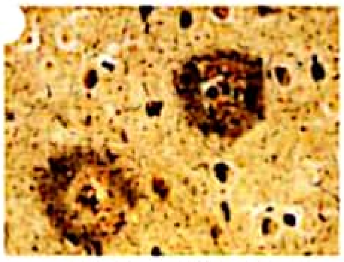


Aβ42 → Key initiator of Cell damage

Aβ40 → a/w Cerebral Amyloid Angiopathy

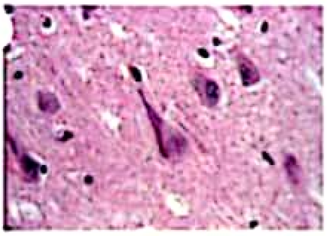
Insoluble Aβ42
⇓
Misfolding of protein → Damage of synaptic neurons in Nu. Basalis of Meyernet
(NT present over here = ACh)
↓
↓↓ Acetylcholine
↓
Dementia / Mental Retradation

- Gross : * Earliest effected area : Medial Temporal lobe
  * Cortical atrophy : → Thinning of Gyri
    → Widening of sulci
    ↓
  * Hydro cephalus ex-vacuo
    Seen in : • Alzheimer's disease
    • Pick's disease



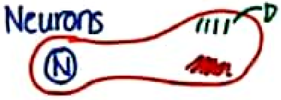
SENILE OR NEURITIC PLAQUES (BIELSCHOWSKI SILVER STAIN)
Neuritic plaques are extracellular accumulations of polymerized β-amyloid centrally with a rim of dystrophic neuritic processes.

- M/E : * Neuritic plaques / Senile Plaques
  • These are dystrophic neurites with amyloid in center
  ↓
  always extra cellular
  • Corelates to severity of dementia
  by : Neuritic Plaque < Neurofibrillary Tangles (BEST)



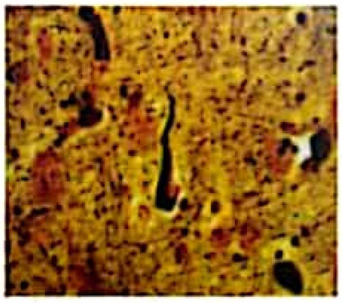
NEUROFIBRILLARY TANGLES
Hematoxylin and eosin stain shows neurons containing flame like filaments known as neurofibrillary tangles (NFTs).

* Neurofibrillary Tangles



→ Tau proteins
↓
Hyper phosphorylation
↓
NFT (Condensed)
• Flame like appearace
• Intra cellular
• After neuronal damage
↓
Extracellular

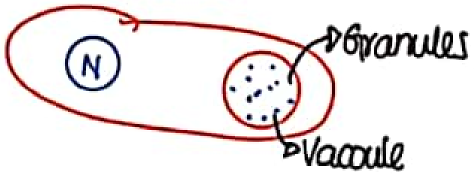
Bielschowsky stain
↓
Sperm like appearance

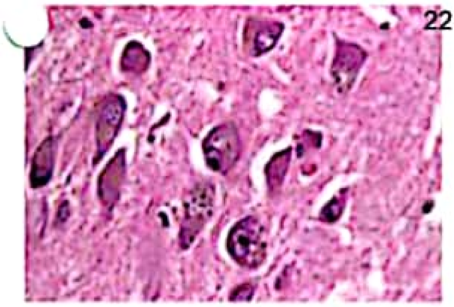


BIELSCHOWSKY SILVER STAIN
showing dark or black flame like neurofibrillary tangles (NFTs).

Scanned with CamScanner

* Granulovacuolar degeneration in neurons

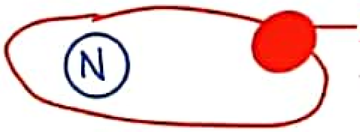




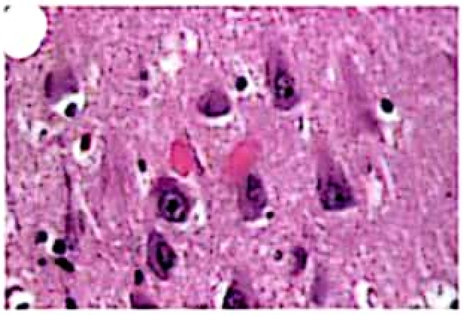
GRANULOVACUOLAR DEGENERATION

Neurons contain basophilic granules surrounded by non-staining vacuoles, termed granulovacuolar degeneration (GVD).

* Hirano Bodies



Eosinophilic inclusion made up of α actin



HIRANO BODIES

They are eosinophilic cytoplasmic accumulations of actin seen in the cytoplasm of hippocampal pyramidal neurons in normal aging and Alzheimer disease.

# MCC of death : Pneumonia (Aspiration)

2. PARKINSONS DISEASE

- aka Paralysis agilaus

# Parkinsonism : Collection of syndrome d/t damage of dopaminergic neurons within basal ganglia

- Parkinsonism :
  Causes : i. MCC Parkinson's Disease (Unknown Etiology)
  ii. Parkinsons syndrome
    - These are 2° to damage of basal ganglia
    - Caused by a) post encephalitic pandemic Influenza infection (1915-1918)
      b) Dopamine antagonists
      c) Pesticides (MPTP)
      d) Repeated Trauma Eg: Boxers
      e) Chronic CO poisoning
      f) Wilson's disease

# Pesticides → ↑ risk
Caffeine, Tobacco } → ↓ risk

- Etiopathogenesis : MC Sporadic > Hereditary

AD
- d/t gene mutations of
  i) α Synuclein
  ii) LRRK-2 (Leucin Rich Repeat kinase)
  iii) GBA (Glucoserebrosidase) a/w Gaucher's disease

AR
- d/t mitochondrial dysfunction.
- Mutation of
  i) DJ-1
  ii) Parkin
  iii) PINK-1

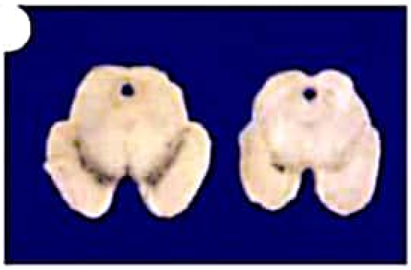
Scanned with CamScanner

- Pathogenesis : Mutations of these genes | Mitochondrial dysfunction | Proteosomal Defect
  ↓
  ↑ α Synuclein protein
  ↓
  more misfolding of protein
  ↓
  damage the dopaminergic neuronal damage
  in Substantia Niagra
  Locus Cerulus

- Clinical Features : * >50yrs
  - * T : Tremor (Pill rolling / Resting tremor)
  - R : Rigidity Cog wheel rigidity
  - A : Akinesia / brady kinesia
  - P : Postural instability with Shuffling gait. aka Festinating gait
  - * Mask like face (expression less face)
  - * dopamine $\xrightarrow[\ominus]{}$ Sebaceous gland.

  In PD ; ↑ sebum → Wax-like face

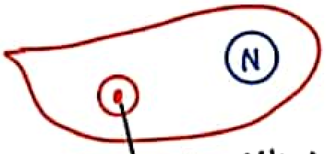
- Gross : • Substantia Niagra ↓ BLACK Colour (d/t dopamine) } (N)
  - • In PD : Pallor of Substantia Niagra correlates the severity



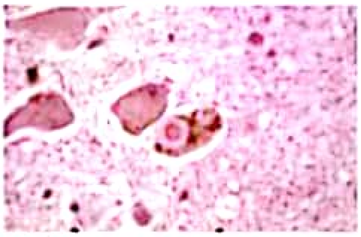
PARKINSON (PALLOR OF SUBSTANTIA NIGRA)

Compared with the normally pigmented substantia nigra on the left there is depigmentation (pallor) of the substantia nigra on the right due to loss of dopaminergic neurons

- MIE :



LEWY BODY
Composed of α-synuclein



LEWY BODY

It consists of a spherical inclusion composed of a dense eosinophilic core surrounded by a pale halo. It contains polymerized α-synuclein

3. HUNTINGTON'S CHOREA / DISEASE

- Male > Female
- 40: 60 yrs
- AD : Chromosome 4 : Trinucleotide Repeat (CAG)

Scanned with CamScanner

Trinucleotide Repeat (CAG)
↓
Excessive amount of Huntington protein
↓
Misfolding
↓
damage of GABAergic neurons of Caudate Nucleus
↓
↓ GABA, ↓ ACh, ↑ dopamine

C/f :
i) Chorea : involuntary purposeless, jerky movement
ii) Dementia
iii) a/w ↓ BDF (Brain derived Neurotropic Factors)

4. AMYOTROPHIC LATERAL SCLEROSIS

- older ; >50yrs
- Etiopathogenesis :
  - AD
  - mutation in SOD-1 (Cu-Zn)

↓
misfolding of proteins
↓
damage of both upper motor neuron & lower motor neuron

- C/f :

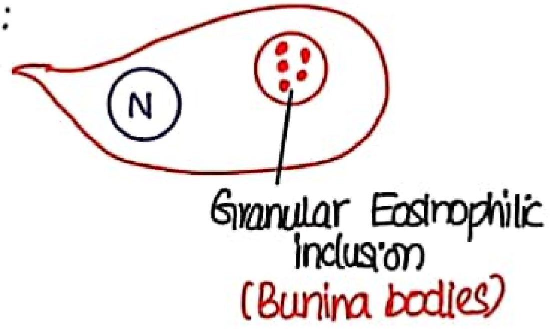
C/f of both UMN & LMN

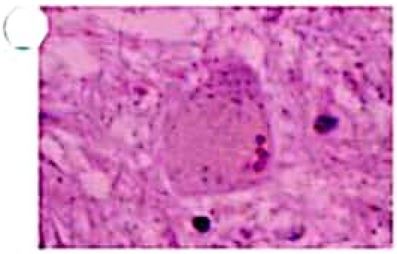
UMN ↓ Hyperreflexia, Spasticity, Paresis

LMN ↓ Muscle atrophy, Fasciculation, Weakness

- Muscle weakness & atrophy of Resp muscle
↓
MCC of death

- M/E:





BUNINA BODIES
Bunina bodies are small eosinophilic intraneuronal inclusions in motor neurons. They are considered as a specific pathologic hallmark of amyotrophic lateral sclerosis (ALS).

BRAIN TUMORS

: MC Brain tumor : Secondaries i.e Metastases.
MC 1° Brain tumor : Meningoma > Glioma
MC Brain tumor in pediatrics : Primary
MC Brain tumor in adults : Secondaries

Pediatric
1. Benign tumor (MC) Juvenile pilocytic astrocytoma
2. Malignancy : Medulloblastoma
3. Overall MC : JPA

Adults
1. MC metastase from Lung Ca (Small cell Ca)
2. Benign Tumor : Meningoma
3. Malignancy : Glioblastoma Multiforme

Scanned with CamScanner

1. Astrocytoma
   - WHO grading :
     - I : Juvenile Pilocytic Astrocytoma
       Sub ependymal Giant cell Astrocytoma (SEGA)
         - origin : Foramen of monro
     - II : Diffuse Astrocytoma
     - III : Anaplastic Astrocytoma
     - IV : Glioblastoma

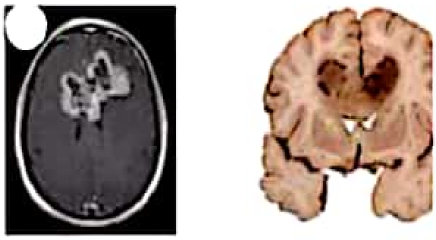
A) Juvenile Pilocytic Astrocytoma
- MC Benign tumor in pediatric age group (MC overall)
- MC Site : Cerebellum
- M/E : i. Neoplastic astrocytes with Rosenthal Fibers
- Surgical t/t is curative in 80 to 100% ∴ Good Prognosis

B) Glioblastoma
- seen in adult.
- MC 1° Malignancy of Brain in adults
- Site of origin : Frontal lobe

WHO - 2016 : Classification : On the basis of Isocitrate Dehydrogenase (IDH)

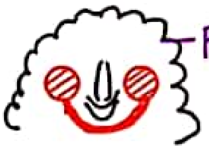
a) Wild Type	b) Mutant Type	c) Not otherwise speci.
* MC Type (~90%) * aka 1° Glioblastoma (denovo)	* 9% * Secondary Glioblastoma Secondary to Diffuse / Anaplastic Astrocytoma	* ~1%
* older age group * MC Mutation : TERT > p53 Telomerase Reverse Trascriptase (TERT)	* younger age group * M Mutation : p53 > TERT	

- Morphology :



GLIOBLASTOMA MULTIFORME
Showing Butterfly wing pattern because tumor crosses the midline via the corpus callosum.

A. Gross :



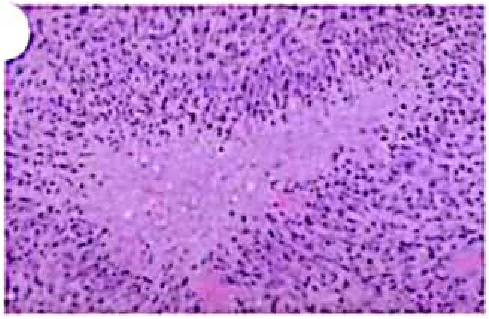
Frontal Lobe : MC site of origin
Bilateral ; Butterfly Glioma
↓
in CT also

B. M/E :

i. ↑ vascular proliferation

} GLOMERULOID BODY

ii) Pseudopalisading Necrosis (dx)



GLIOBLASTOMA MULTIFORME
Showing "pseudopalisading necrosis (serpentine necrotic area are pushing tumor cells at their edges).

Palisading

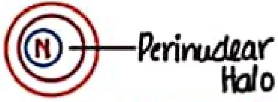
TRUE
Cell arrangement is parellel to each other

FALSE/PSEUDO
When necrosis induces palisade

WORSE PROGNOSIS FOR GLIOBLASTOMA

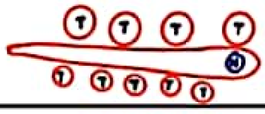
2. Oligodendroglioma
- Age group : 40-50yrs
- MC Site : Cerebral Hemisphere (White matter)
- Gross : Gelatinous & areas of calcification
  May have hemorrhages
- M/E :

i) Fried egg Tumor Cell



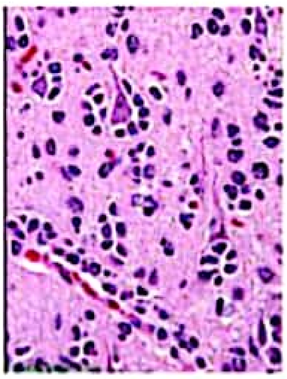
ii) Anstomosing B.V

iii)

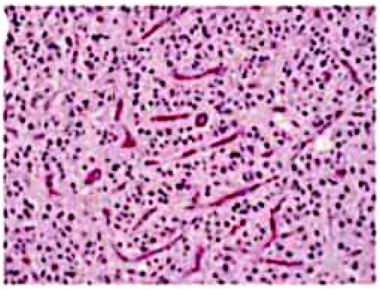


Perineuronal Satellitosis

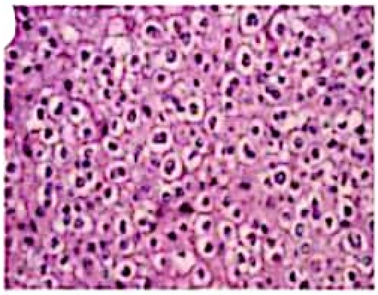
- Molecular Cytogenetics : Loss of hetrozygocity Chr 1p & 19q
  ∴ responsive to chemotherapy
  ∴ Good prognosis



OLIGODENDROGLIOMA
Tumor cells spread along pathways of least resistance, resulting in perivascular and perineural accumulation of tumor cells (perineuronal satellitosis).



OLIGODENDROGLIOMA
Tumor cells closely resemble normal oligodendrocytes, with regular round nuclei surrounded by perinuclear halos giving appearance of "fried egg".



OLIGODENDROGLIOMA FRIED EGG
Tumor cells closely resemble normal oligodendrocytes, with regular round nuclei surrounded by perinuclear halos giving appearance of "fried egg".

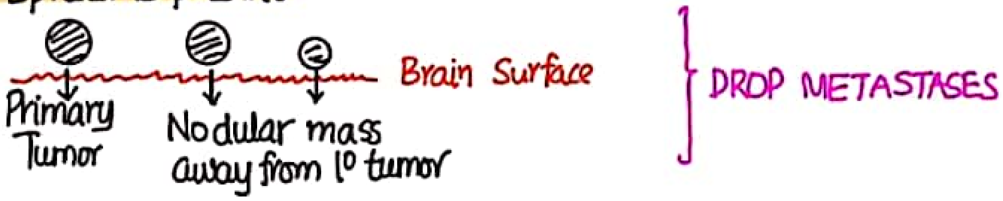
3. Apendymoma
- origin : ventricular lining
- In pediatric age group origin : Floor of 4th ventricle
  ∴ CSF metastasis chance

In adult age group origin : Spinal cord (Filum terminale)
⇓
a/w Neurofibromatosis-2 gene mut. (NF)

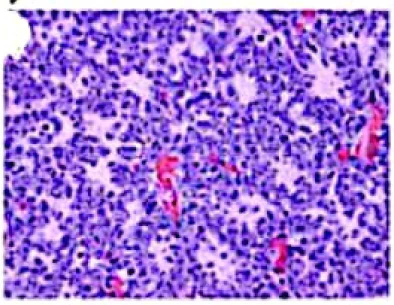
4. Undifferentiated Medulloblastoma

↓ as both glial & neuronal components are present

- MC malignancy of brain in Pediatric
- MC Site: Cerebellum
- CSF spread is present



- WHO 2016 : Classification
  - i. WNT Type : * mutation in WNT signalling pathway
    - * Good prognosis
    - * a/w a) Monosomy
    - b) α-Catenin
  - ii. SHH Type : * mutation in SHH pathway → • Medulloblastoma • Basal ca of skin
    - * N-myc amplification
    - * Intermediate prognosis
  - iii. Group III Non WNT/ No SHH : * MYC amplification + isochromosome 17q (i17q) } WORSE PROGNOSIS
  - iv. No MYC amplification : * no myc amplification
    - * But i17q present
    - * poor prognosis

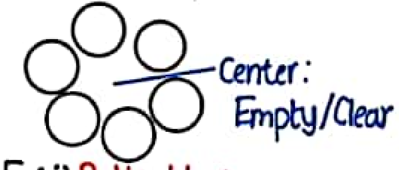


MEDULLOBLASTOMA
Showing small round blue tumor cells with Homer-Wright pseudo-rosettes (groups of tumor cells arranged in a circle around a fibrillary center).

- M/E : i. Both glial + Neuronal element
  - ii. Homer wright pseudo rossette

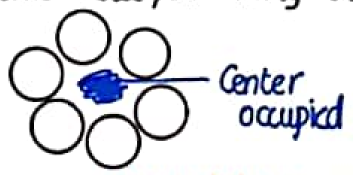
Rossette

True
Tumor cell arranged like flower petal



Eg: i) Retinoblastoma
Flexner wintersteiner
ii) Ependymoma
Both true & pseudo

False
Centeral part with Tumor mass, BV or any other structures



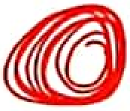
Eg: i) Medulloblastoma
ii) Neuroblastoma } Homer-wright Pseudrosette
iii) Pinelo blastoma
iv) PNET

- Molecular cytogenetics :

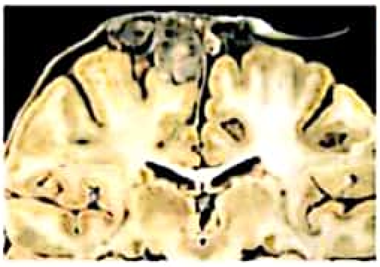
GOOD	BAD
* Trk-C expression * β catenin expression	- N-MYC amplification

- Radiosensitative ; excision is curative

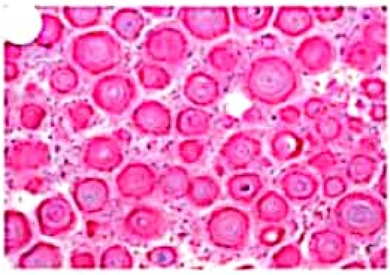
5. Meningioma
- MC Benign tumor in adults
- Site of origin : Arachinoid cap cells (= Meningothelial Cells)
- Molecular cytogenetics : NF-2 gene mutation on Chr. 22.
- Gross : i. duramater based tumor
  ii. On cutting : GRITTY d/t Psammoma Calcification
- M/E :



Tumors in whorl like structure
+
Psammoma Bodies



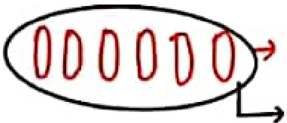
MENINGIOMA (GROSS)
Gross: Dura based tumor causing compression of underlying brain tissue.



MENINGIOMA (LM)
Microscopy of tumor shows whorled pattern of cell growth and calcified psammoma bodies

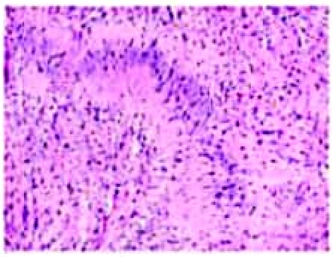
- 1. Fibro blastic
  2. Psammoma
  3. Anaplastic : WORSE PROGNOSIS
  F Meningothelial
  } Histological variants
- F > M : ↑ progesterone receptor expression on tumorcell
  ↓
  ∴ Grow during pregnancy

6. Schwannoma
- aka Accoustic neuroma (=arising from 8th cranial nerve)
  ↓
  MC Site : Inferior vestibular branch
- a/w NF-2 gene mutation
- M/E : * Antoni - A
  * Antoni - B



→ Palisading of cell : Cellular Area → Antoni A
↳ Verocay Bodies

→ Hypo cellular Area : Antoni-B



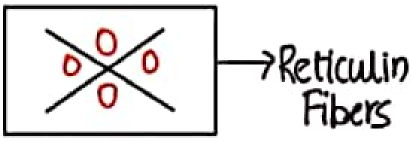
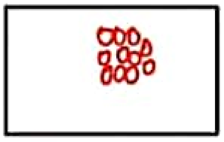
SCHWANNOMA (VEROCAY BODIES)
Showing peripheral palisading of nuclei called as verocay bodies. Two areas seen histologically

Two areas seen histologically.
a) Cellular is "ANTONI-A" areas contain Verocay bodies.
b) Hypocellular is "ANTONI-B".

Primary CNS Lymphoma

- Adults : MC Site : Frontal lobe
- These are DLBL (B cell Lymphoma)
- a/w ↓ immunity Eg : AIDS
- a/w Latent EBV infection
- Surgical treatment is not curative
  ↳ only for tissue diagnosis

—M/E :

1° CNS Lymphoma	2° CNS Lymphoma
* Reticulin stain :	* Reticulin stain :
	
individual tumor cell is seperated individually HOOPING SIGN ⊕	Cluster of tumor cell present Hooping Sign ⊖

Brain tumors

GLIAL TUMORS
- i) Astrocytoma
- ii) Oligodendroglioma
- iii) Ependymoma

Neuronal Tumors
- i. Ganglioglioma
- ii. Ganglio cytoma
- iii. Neuro cytoma
- iv Dys embryoplastic Neuro epithelial Tumor

Undifferentiated
- Medulloblastoma

Meningical
- i) Meningioma

Miscellaneous tumors : # 1° CNS Lymphoma
Extragonadal Germ cell tumor
MC site : Mediastinum (overall)
MC site in brain : Pineal gland.

GASTROINTESTINAL TRACT

LAYERS OF GIT

Mucosa	Epithelium, Lamina Propria, Muscularis mucosa
Submucosa	Meissner's plexus
Muscularis Propria	Aurebach plexus
Adventia (esophagus) / Serosa (for other struct)	

# strongest layer of GIT : Submucosa

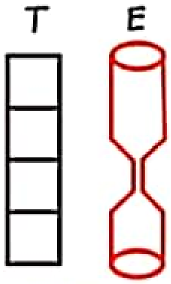
ESOPHAGUS

I : TRACHEO-ESOPHAGEAL FISTULA

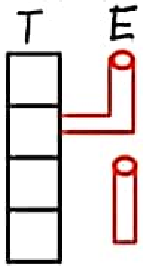
* Tracheo-eosophageal ridges fusion In 4th week of IU life
⇒ Failure of fusion of tracheo-esophageal ridges
↓
Tracheo-esophageal Fistula

* C/f : i) Newborn with onset of feeding
↓
Starting Chocking → Coughing → Vomitting → Cyanosis
ii) Excessive salivation

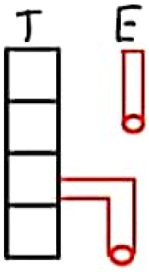
* TEF are of 5 types



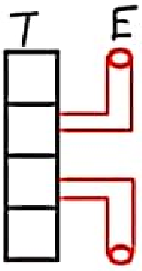
TYPE-A
* only E-atresia
* No TEF



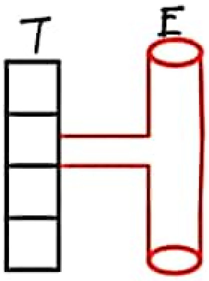
TYPE B
* proximal TEF
* E-atresia



TYPE-C
* proximal E-atresia
* distal-TEF
* Most common type



TYPE-D
* proximal TEF
* distal TEF



TYPE-E
* No E-Atresia
* TEF only ⊕
* aka H Type

II : EOSOPHAGEAL DIVERTICULA

* Herniation or outpouching of E-layers through the wall.
* ↑ intraluminal pressure leads to Herniation of E-wall

Scanned with CamScanner

* Constrictors of Eosophagus = 3 types
# Length of E = 25cm

First constriction : Cricopharyngeal constrictors at 15 cm
Second constriction : Aortic/Broncheal constrictors at 25cm
3rd constriction : Epiphrenic constrictors at 40cm

* Outpauching at First Constriction : Zenkers diverticulum
- It's a pseudo diverticulum
- ∵ E. mucosa or submucosa is outpouching only

Outpauching at 2nd Constriction : Traction diverticulum
- d/t Mediastinal Fibrosis
  Diffuse E-spasm
- all layers form outpauching
  ∴ TRUE diverticulum

Outpauching at 2nd Constriction : Epiphrenic Diverticulum
- Only mucosa/submucosa is herniating
  ∴ PSEUDO DIVERTICULUM
- Risk : Esophagitis
  GERD
  Achalasia

II. ACHALASIA

- d/t loss of inhibitory neurons

↓ control

NO & Vasoactive Intestinal Polypeptide (VIP) release

↓

These causes relaxation of LES sphincter

- In Achalasia ↓NO & ↓VIP ⟶ Loss of relaxation of LES sphincter
- Clinical Features : Triads
  - i) ↑ LES tone
  - ii) No relaxation of LES
  - iii) Aperistalsis of Esophagus
  - * difficulty swallowing of both solid & Liquid food
- Types of achalasia : A) Primary (Unknown)
  d/t degenerative changes in neurons
  B) Secondary
  d/t i) Infections
  Eg: Chagas disease : Trypanasoma cruzi
  ii) DM (Autonomic nerve damage)
  iii) Infiltrative disease : Malignancy / Amyloidosis
- Complications : • GERD
  • Barrett's Esophagus
  • Esophageal cancer

TRAUMATIC DISORDERS OF ESOPHAGUS

A. MALLORY WEISS TEAR

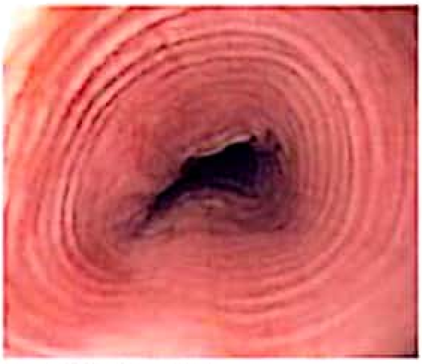
- Alcoholics → Forceful vomiting
  ↓
  Trauma
- nature of damage : Less severe
  Vomitting is against delayed relaxation of Cardia
- only Mucosal tear ⊕
  i.e Superficial Rupture
  ↓
  Spontaneous Healing
- MC Site : Gastro - Esophageal Junction
  (Cardia of stomach)
  ↓
  Lesser curvature
  Longitudinal tears are present

B. BOERHAAV SYNDROME

- Alcoholics → Forceful vomiting
  ↓
  Trauma
- nature of damage : severe
  Vomitting against clossed glottis
- all layers will be ruptured
  ∴ more severe
  ↓
  Require Surgical treatment
- MC Site : Left posterolateral Lower ⅓rd Esophagus
- Food spillage in Mediastinum
  ↓
  Mediastinitis

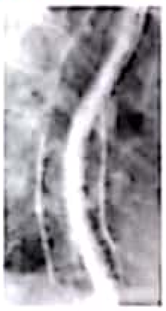
FELINE ESOPHAGUS

- aka Eosinophilic Esophagitis / Allergic Esophagitis
  bcoz it's a/w Eosinophilic Inflammatory infiltarate
- MC a/w Eosinophilic Esophagitis
- C/f : * diffulty in swallowing
  * vomitting
  * Gastro Esophageal Reflux
  * Food impaction
- Double contrast Esophagogram : showing concentric mucosal thickening
  ↓
  Herring Bone Pattern
- Endoscopy : concentric mucosal thickenning
  d/t Eosinophilic infiltarate
  These type of Esophagus present in Cats.
  aka Trachealisation of Esophagus
- Biopsy : Diagnostic ∵ ↑ amount of E°- infiltarates
  (>15 Eosinophil/HPF)



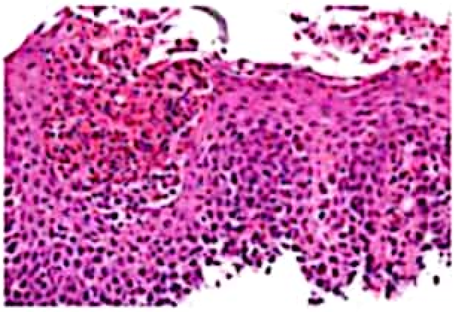
FELINE ESOPHAGUS*

Showing concentric mucosal rings (called trachealization or felinization because of its resemblance to the trachea or cat esophagus).



FELINE ESOPHAGUS (DOUBLE CONTRAST ESOPHAGOGRAM)

Showing radiolucent folds across the esophagus forming angle with respect to the center of the esophagus in a "herring-bone" pattern.



FELINE ESOPHAGUS

Biopsy showing dense eosinophilic infiltrate within superficial epithelial lining of the esophagus, and forming microabscesses at places

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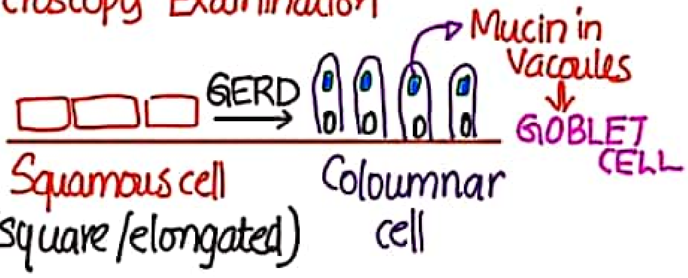
BARRETT'S ESOPHAGUS

- Male : 30-50yrs old
- MC a/w GERD
- Morphology

A. Gross (= Endoscopy)
i) Reddish mucosa (Salmon pink colour) in Lower 1/3rd of Mucosa

B. Microscopy Examination

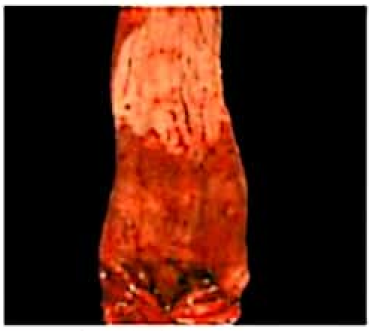


Coloumnar Metaplasia

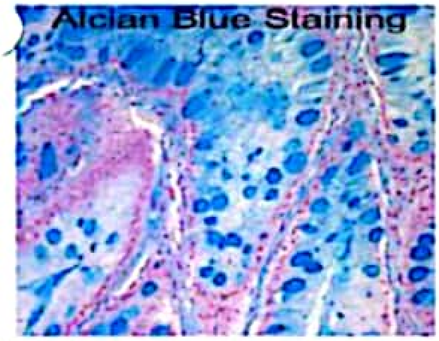
Mechanism : Stem cell reprogramming
aka : Intestinal metaplasia (Hallmark)

Special stain : Alcian Blue stain (pH= 2.5)
↓
Mucin (Blue)

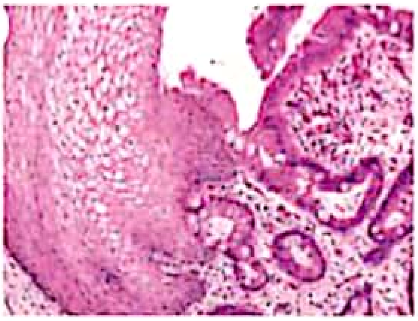
- Risk : Esophageal Adenocarcinoma



BARRETT'S ESAPHOGUS
Gross appearance showing velvety, salmon-colored mucosa extending above the gastroesophageal junction.



BARRETT'S ESAPHOGUS
Alcian blue stain of Barrett's mucosa shows the blue-staining goblet cells, a few specialized columnar cells, and the clear-staining gastric-type surface columnar cells



BARRETT'S ESAPHOGUS
Biopsy showing columnar metaplasia on the left and esophageal stratified squamous epithelium on the right.

ESOPHAGEAL TUMOR

- MC Benign tumor : Leiomyoma
- MC Malignancy : Squamous Cell Ca > Adeno Ca.
- MC Site for Sq. cell ca ⇒ Middle 1/3rd of E
  MC Site for Adeno ca. ⇒ Lower 1/3rd of E

ESOPHAGEAL SQ. CELL CA.

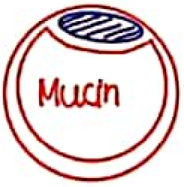
- Male : 40-60 yrs
- Dysphagia, Vomitting, Hemetemesis
  Lump in Esophagus
- Risk factors : · Smoking
  · Alcoholism
  · Salted & Preserved food
  · Nitrites (in pickles)
- also a/w Plummer wilson Syndrome
  i) Iron def. Anemia
  ii) Esophageal web
  iii) Glossitis
- it's also a/w Vit A,C,E deficiency
  Micronutrient def. (Selenium, Zinc, Molybdenum)
- Human Papilloma Virus in
  Endemic area : ↑ risk
  Non-endemic : No risk
- Gross : Middle 1/3rd of E
  ↓
  Ulceration / Polyp like mass

- M/E : Well differentiated / Moderately differentiated / Poorly differentiated
  ↓
  MC
- MC paraneoplastic syndrome : Hypercalcemia

ESOPHAGEAL ADENOCARCINOMA

- Male : 40-60yrs
- a/w Barret's Esophagus
  GERD
- Pathogenesis :
  GENETIC & EPIGENETICS
  ↓
  Mutation {
  - p53
  - RB Gene
  - p16 INK4a

- M/E : Adenocarcinoma
  - Intestinal Type
    * Tumor cells forms glands like Intestine
  - Diffuse Type
    * noglandular pattern
    * may observe SIGNET RING CELL



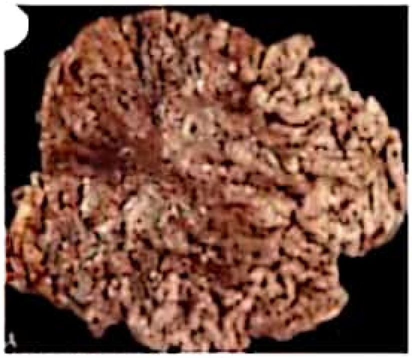
STOMACH

A. GASTRITIS	B. GASTROPATHIES
- mucosal damage with inflammation	- mucosal hypertrophy with minimal/no inflammation

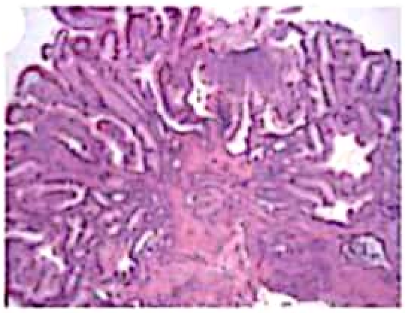
GASTROPATHIES

I. MENETIERS DISEASE

- Young Male
- Basic pathology : ↑ TGF-α → Mucosal Epi. Hyperplasia
  ↓
  Enlarged Rugal Folds
  ↓
  looking like Brain surface
- C/f :
  - Loss of protein (Hypoproteinemia)
  - ↑ risk for Gastric adenocarcinoma
- Gross : i) Enlarged Rugal Folds
  ↓
  Cerebriform Rugal folds
- M/E : I) Foveolar epithelial cell hyperplasia
  II) Cystic dialation of glands
  III) minimal/no inflammation
- Risk : transformation to Gastric adenocarcinoma



MENETRIERS DISEASE
Gross : The rugal folds are diffusely enlarged.



MENETRIERS DISEASE
Microscopy showing foveolar hyperplasia with elongated and focally dilated glands.

GASTRITIS

- mucosal inflammation & damage.
- Can be i) ACUTE
  ii) Chronic

Scanned with CamScanner

- Etiopathogenesis:

A) ACUTE GASTRITIS
i) Drugs : NSAIDS
ii) Alcohol
iii) Smoking
iv) Stress

B) CHRONIC GASTRITIS
i) Autoimmunity
it's aka Type-A Gastritis
ii) H. pylori infection (MC Type)
it's aka Type-B Gastritis

- Pathogenesis: Gastritis is d/t damage of mucosal defence mechanism

Normal Mucosal Defence Mechanisms

Increase Mucosal Blood Flow
↓
Protected by
i) absorption of excessive amount of Acid
ii) Secretion of Bicarbonates
iii) help in Mucin secretion

Prostaglandin synthesis
↓
Protected by
i) ↑ mucin synthesis
ii) ↑ perfusion of mucosa
iii) ⊖ acid production

- Acute Gastritis

- Gross : Hypermia ⊕
- M/E : Superficial Ulceration
  Neutrophilic infilterate
- Stress induced Gastritis

- Stress → Local Ischaemia (most important)

1) Stress due to Brain injury
↓
⊕ Vagal nerve
↓
↑ gastric acid secretion
↓
Ulceration & damage

2) Because of damage
↓
Release of Endothelin
↓
Vasoconstriction
↓
Ischaemia

- ∴ Reason for Stress Ulcers : Systemic acidosis + local ischaemia + gastric hypersecretion

- Stress Ulcers are of 2 types

Cushing Ulcer
* It's d/t Head injury
* MC site : Stomach (Cardia)
* Single deep ulcers ⊕
↑ risk of perforation

Curling Ulcer
* it's due to Burns
* MC Site : Proximal duodenum
* Multiple small superficial ulcers
↓ risk for perforation

- Chronic Gastritis

- It's due to Autoimmune disease & H. Pylori infection

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CHRONIC GASTRITIS

Autoimmune Disease
(TYPE-A)

* MC Site : Body of stomach
* CD_4 TH_1 form Antibody

↓ damage

Parietal Cells & IF

↓ Gastric HCl (achlorhydria) ↓ Vit B_{12}

↓

⇒ Hyper Gastrin

⇒ 2° Bystander mechanism

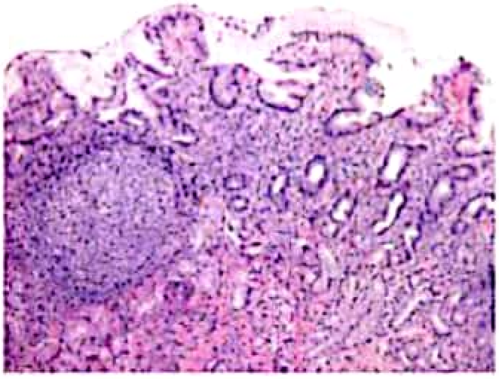
↓

damage of chief cell

↓

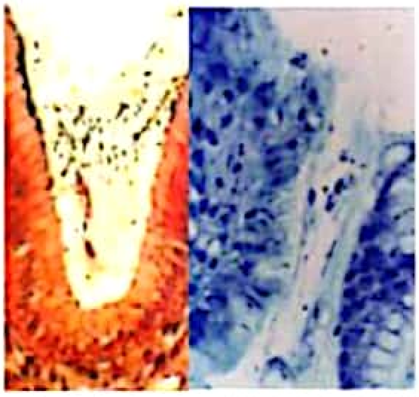
↓ Pepsinogen 1

* Risk : Atrophic gastritis
↓
Then Adeno carcinoma



GASTRITIS (H. PYLORI)

Lymphoid aggregates with germinal centers and abundant subepithelial plasma cells within the superficial lamina propria are characteristic of H. pylori gastritis.

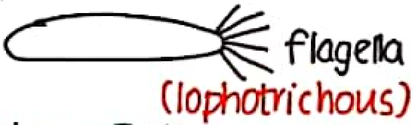


WARTHIN-STARRY STAIN AND GIEMSA STAIN

highlights the small curvilinear organisms (H. pylori) at the foveolar surface

H·Pylori infection
(Type-B)

* MC Site : Antrum (lesser curvature)
* H·pylori G-ve Bacteria



* Virulence Factors :
i) Production of Urease
↓
Production of NH_3
↓
Buffering of gastric acid
ii) Adhesin molecule
help in adhesion
iii) Cytotoxic genes
CAG-A / VAC-A
help in damage of gastric epithelial cells.
* Morphology :
• gastric mucosal damage ⊕
↓
Ulceration + Fibrin exudates
• Inflammatory infiltarate (Lymphoplasmacitic)
• Lamina Propria showing Dense lymphoplasmacitic infiltarates
$\underbrace{\qquad\qquad}$
Forming Lymphoid aggregates with germinal centers
* Best non-Invasive investigation : Serology
* Best investigation : Gastric Biopsy (invasive)
↓
Rapid urease test

Special Stain

- Silver Based
  - Warthin Starly
  - ↓
  - dark spiral bacilli
- Non-silver Based
  - i) Giema
  - ii) Giemnez

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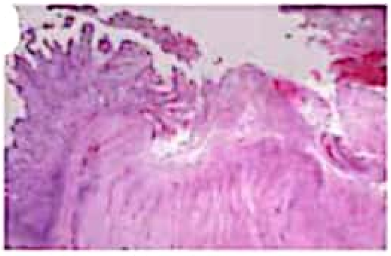
PEPTIC ULCER DISEASE

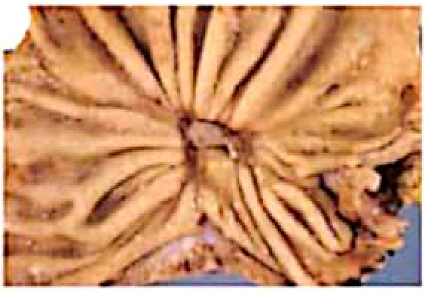
- One of the complication of Chronic gastritis
- Pathogenesis : Damage of mucosal defensive mechanism

Ulcer : seen in Gastric & duodenal ulcer

Gastric Ulcer	Duodenal ulcer
* MC Site : Antrum Lesser curvature near incissura angularis	* MC Site : Proximal duodenum
* C/f : · Abdominal pain (Random) · Pain relieved by vomitting · Loss of weight · Hematemesis	* C/f : · Abdominal pain (Night) · pain relieved by taking food. · No loss of weight · Malena
* Complication : · perforation (MC) · ↑ risk of malign. transformation	* Complication · Bleeding (MC) · No risk of Malignant trans.



GASTRIC ULCER
Microscopy showing classic appearance of peptic ulcer with superficial fibrin exudate over necrosis, followed by granulation tissue and fibrosis in the deep aspect.



GASTRIC ULCER
Gross: Gastric ulcer is showing characteristic sharp demarcation from the surrounding mucosa, which has prominent radiating folds.

* MCC of Death in Peptic Ulcer disease : Bleeding

- Gross : · Sharp punched out ulcer
  · Mucosa over hanging & forming radiating folds
- M/E : · Ulceration
  · Fibrinous exudates

STOMACH TUMORS

- MC Benign tumor of stomach : Adenoma
- MC Malignant tumor (or)
- MC Epithelial malignant tumor of stoma
  } Gastric adenocarcinoma

GASTRIC ADENO CARCINOMA

- Male >50yrs
- Risk factors :
  - (a) Environmental Factor
    - Hpylori infection
    - Smoking
    - Nitrites
    - Smoked/Salted food
  - (b) Host factor
    - Barret's mucosa
    - Menetrie's disease
    - Blood group - A : a/w Cancer
    - # Group O : Ulcer
  - (c) Genetic Factor
    - CDH-1 gene mutation (MC)
      ↓
      E-cadherin
      ⇓
      Familial gastric Adenocarcinoma
    - p53 gene muta.
    - TGF-β

MC Site : Antrum (lesser curvature)
MC site metastases : Liver

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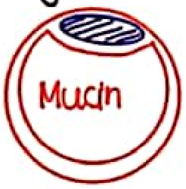
- Pathogenesis : Loss of intercellular adhesion (most important step)
  ↓
  d/t mutation in CDH-1 gene (E-cadherin)
- Classification : Based on

A) Depth of invasion

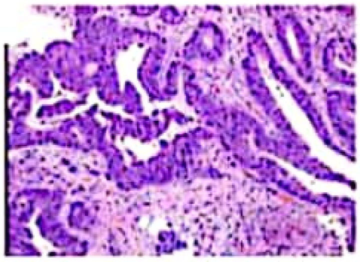
- Early
  * Involvement of Mucosa + Submucosa ± LN involvement
- Late
  * Tumor is infiltrating beyond Submucosa

B) Histology

- Intestinal
  * gland like intestinal
  * a/w H.pylori inf. (intestinal > diffuse)
  * In last 20yrs incidence is reduced d/t effective H.pylori t/t
- Diffuse
  * arranged in sheets

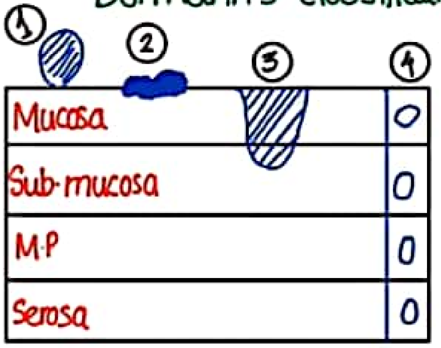


Signet rings ⊕
  * a/w H.pylori infe.

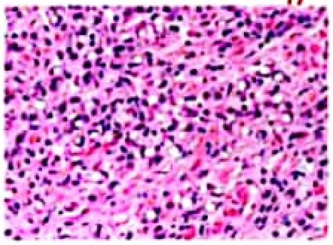


GASTRIC CARCINOMA (INTESTINAL TYPE)
Microscopically, there are innumerable poorly formed glands replacing mucosa in the intestinal-type carcinoma.

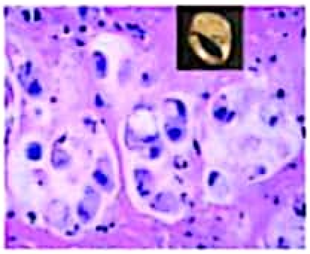
C) Growth Pattern / Bormann's classification



① Exophytic : polyp like protrusion
② Flat or infiltarative
③ Ulcerative
④ Linitis plastica
  - All 4 layers tumor infil.
  - Leather Bottle like app



GASTRIC ADENOCARCINOMA (DIFFUSE TYPE)
Tumor cells have large intracytoplasmic vacuoles that push the nucleus to the periphery creating a signet ring appearance



GASTRIC ADENOCARCINOMA
Tumor cells have large intracytoplasmic vacuoles that push the nucleus to the periphery creating a signet ring appearance

GASTROINTESTINAL STROMAL TUMOR (GIST)

- MC mesenchymal tumor of GIT
- Male : 40-60 yrs
- MC presentation : Bleeding > Pain
- MC site for GIST : Stomach > Intestine
- a/w
  - Neurofibromatosis-1
  - Carney's Triad : GIST (gastric)
    Paraganglioma
    Pulmonary chondroma
  - Carney's Stratakis Syndrome
    - d/t germline mutation in SDH gene (Succinate Dehydrogenase)
    - Consist of GIST + Paraganglioma
    - SDH A/B/C mutation
    - SDH B mutation is a/w Pediatric GIST
      ↓
      No CKIT/PDGFR-α mutation
- Origin : Interstitial cells of Cajal in muscularis propria (Pacemaker of GIT)
  ↪ as it control peristalsis

- Histologically it can be
  - A) Epithelioid type
    - * seen only in Gastric region.
  - B) Spindle pattern (MC)
- Usually it's a benign tumor
  - Features of Malignancies:
    - i) Size >5cm
    - ii) Mitotic figure >10/HPF
    - iii) Lobular contour with area of necrosis
    - iv) Liver or peritoneal metastases

    } Poor Prognosis
- IHC markers :
  - i) CKIT mutation (MC)
  - ii) PDGFR-α mutation
  - iii) DOG-1 (Design only for GIST) : Most specific IHC
    - → i) covers both C-KIT mutation & PDGRF-α mutation
    - ii) Covers metastatic GIST also.

INTESTINE

DISORDERS OF MALABSORPTION & DIARRHEA

A) INFECTIVE

- i) Tropical Sprue
- ii) Whipple's disease
- iii) Amebiasis
- iv) Giardiasis
- v) Pseudomembranous collitis

B) NON INFECTIVE

- i) Celiac disease
- ii) Inflammatory Bowel disease (IBD)
  - a) Crohn's disease
  - b) Ulcerative collitis

TROPICAL SPRUE

- Seen in Tropical countries
- 40:60 yrs
- C/f : Malabsorption

  ↓

  Stool examination :
  - # Excessive fecal fat
  - # greasy
  - # malodourous
- MC d/t E. Coli infection
- Biopsy Non diagnostic

  ↳ showing villous atrophy
- MC Site : Ileum

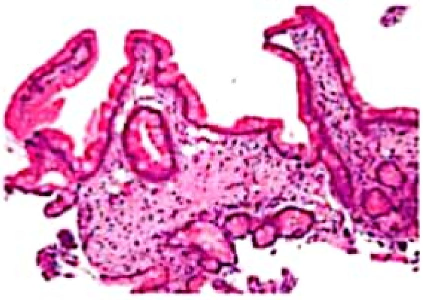
  ↓

  ∴ prone to develop Megaloblastic Anemia

WHIPPLE'S DISEASE

- Infection caused by Tropheryma whippelei (G +ve Actinomycetes)
- MC Site : Small intestine
- C/f : Malabsorption + CNS Involvement
- Biopsy diagnostic
- M/E : i) Small intestine Lamina propria with collection of macrophages containing Bacteria in Lysosome
  - ii) Bacterias are PAS +ve

    Diastase Resistant



WHIPPLE DISEASE

H&E stain. Duodenal biopsy. The images show the characteristic feature of Whipple's disease; foamy macrophages are present in the lamina propria.

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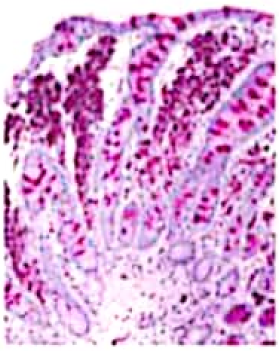
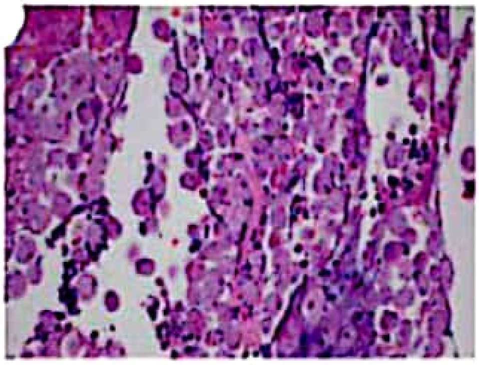
# intestine contain Glycogen → PAS+ve
In whipple's disease Bacteria → PAS +ve
But diastase resitant.
Whereas Glycogen is diastase sensitive



WHIPPLE DISEASE.
Periodic acid-Schiff (PAS) stain macrophages contain periodic acid-Schiff (PAS)-positive, diastase-resistant granules that represent lysosomes stuffed with partially digested bacteria.

AMEBIASIS

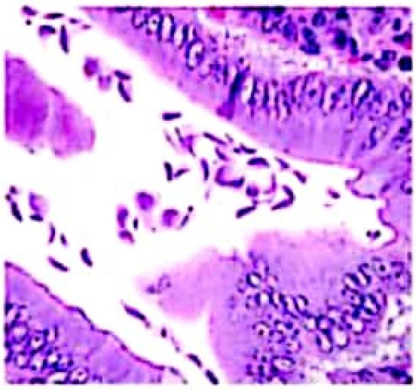
- caused by protozoal infection E. histolytica
- C/f : Dysentry, Malabsorption
- MC Site : Cecum
- M/E : i) mucosa & submucosal ulceration
  narrow at mucosa
  broad at submucosa
  ↓
  Flask shaped Ulcers
  ii) Trophozoite of Entameba
  ↓
  macrophage like appearance
  - round oval cells
  - central prominent nuclei
  - erythrophagocytosis present



ENTAMOEBA HISTOLYTICA
Colon biopsy showing organisms (amebae are similar to macrophages in size and general appearance) ingesting red blood cells.

GIARDIASIS

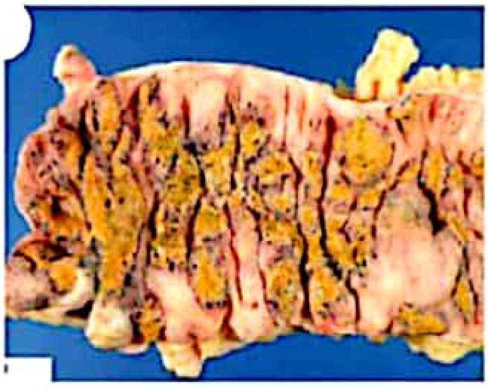
- caused by parasitic infection
- spread : contaminated food/fecal
- a/w Immunodeficient patient (↑ Risk)
- MC Site : Small intestine
- Biopsy is diagnostic
- M/E : · Trophozoites present
  · Binucleated & pear shaped
  ↓
  histopathologically : Pear shaped
  Comma shaped
  Sickle shaped



GIARDIASIS
Malabsorption case biopsy showing luminal space of small intestine with "pear shape" or "Sickle-shape" Trophozoites.

PSEUDOMEMBRANOUS COLLITIS

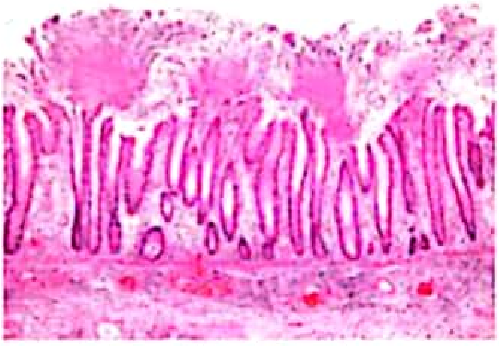
- aka Antibiotic associated diarrhea
- MC a/w 3rd gen cephalosporin
- ↑ colonisation by Clostridium defficile (mc/classical)
  Toxin → Epithelial damage /Ulceration
  ↓
  after that covered by fibrinous exudates
  & inflammatory cells
  ↓
  Pseudomembrane formation



PSEUDOMEMBRANOUS COLITIS
Gross: mucosal surface of the colon is hyperemic and is partially covered by a yellow-green exudate.

Scanned with CamScanner

- It can also a/w Salmonella
  Staphylococcal
  Cl. perfringes
  Ischaemic collitis
- Gross : Cut section :
  Yellowish green exudate covering mucosa
- M/E : • Ulceration + fibrinous exudates + inflammation
  ↓
  Pseudomembrane formation
  Volcano pattern of fibrinous exudates



PSEUDOMEMBRANOUS COLITIS
Microscopy shows classic "volcano" pattern of fibrinopurulent exudate erupting from the superficial mucosa and layering out over the ulcerated mucosal surface

CELIAC DISEASE

- non-infective cause of malabsorption
- aka Celiac sprue
- Autoimmune disorders
- In pediatric : M=F
  In Adults : F>M
- It's immune mediated diarrheal disorder caused by Gluten protein in cereal
  B - Barlie
  R - Rye
  O - Oats
  W - Wheat
- Pathogenesis :
  immune cell mediated mucosal damage
  ↓
  $CD_4 T_{H1}$ & CD_8 T

Cereal → Gliadin → indirect mechanism

⊕ ↓ ↑ IL-15 expression on mucosa
⊕ ↓ proliferation & diff. of CD_8 T cells
Enterocyte damage by apoptosis

indirect mechanism:
Trans glutaminase deamidation of Gliadin
↓
Deamidated Gliadin (Ag)
↓
presented to $CD_4 T_{H1}$ by HLA DQ-2/8
↓
activation of $CD_4 T_{H1}$
↓
Cytokine synthesis
↓
Enterocyte damage

- Diagnosis : Biopsy : Non diagnostic & Non specific
  Multimodality Approach
  1. H/o gluten sensitive Cereals
  2. Endoscopic Biopsy : • Atrophy of villi
     • similar amount of Cryptic hyperplasia
     • Overall mucosal thickness remain same

- Cryptitis is absent [present in
  - IBD
  - Inf. enterocolitis]

- In epithelial cell → Lymphocytic infilt.
  ↓
  Epithelial damage
  called as Lympho epithelial lesion
  ↳ CD8 T cell
  ↓
  ↑ risk of Lymphoma (MC T Cell Lymphoma
  ↓
  aka Enteropathy associated T Cell Lymphoma

3. Serological Examination
M.Sensitive : IgA Ab against Transglutaminase
M.specific : IgA/IgG anti-Endomycial Ab

- MC Site : Proximal duodenum (Most severly effected area)
  ↓
  ∴ ↑ risk for Iron deficiency anemia
- Risk : i) IDA
  ii) T cell Lymphoma
  iii) Small intestinal adenocarcinoma
  iv) Esophageal sq. cell carcinoma

INFLAMMATORY BOWEL DISEASE

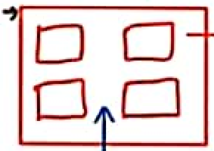
- A.I ; F > M ; 20-40 yrs
- Basic Etiology : Mucosal immunity defect.
  Hygeine Hypothesis
  - ↑↑ Hygeine ⟶ Ⓝ Gut Bacterio dead → No-development of mucosal immune
    ↓
    IBD
- It's of 2 types :

A) CROHN'S DISEASE	B) ULCERATIVE COLITIS
- a/w $CD_4 TH_1$ cell → ∴ Granuloma ⊕	- a/w $CD_4 TH_2$ → E°/Mast cell infil.
- HLA DR-1	- HLA DR-2
- MC site : Terminal Ileum Rectum will be spared.	- MC site : Rectum
- Earliest GI manifestation : Apthous Ulcer	- Earliest GI manifestation : Apthous Ulcer
- Gross : • Skip lesions ⊕ • Mucosal regeneration ↓ Pseudopolyp formed (patchy distribution) Pseudopolyp is never premalignant • Creeping mesenteric fat	- Gross : • Continous mucosal lesions ⊕ • Mucosal regeneration ↓ Pseudopolyp formed (diffuse distribution) Pseudopolyp is never premalignant

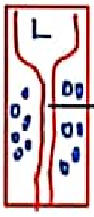
Scanned with CamScanner

A) CROHN'S DISEASE

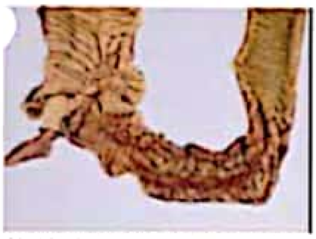
- Gross :
  - Cobble stone appearance



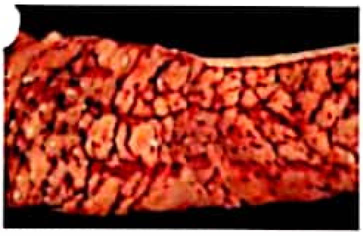
linear/deeper ulceration

- 

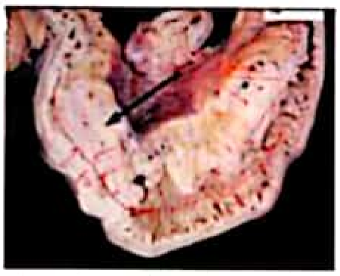
Narrowing of Lumen d/t Fibrosis & Calcification
⇓
On radiological Examination
String sign of Kanator



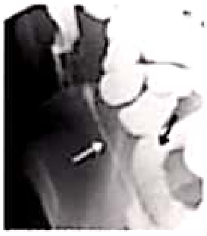
CROHN'S DISEASE (SKIP LESION): CHARACTERISTIC SKIP LESION
showing sharp demarcation between the cobblestone mucosa of the involved segment and the grossly normal ileal and colonic mucosae.



CROHNS DISEASE (COBBLESTONE" APPEARANCE)
Showing islands of edematous mucosa surrounded by linear ulceration showing the classic "cobblestone" appearance of Crohn disease.



CROHN'S DISEASE ('STRING SIGN OF KANTOR)
Showing terminal ileum with luminal stenosis and severe stricture giving classical 'string sign of Kantor' appearance.



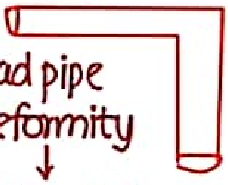
CROHN'S DISEASE ('STRING SIGN OF KANTOR)
Showing linear fraying of the column of barium study of the terminal ileum with luminal stenosis and severe stricture giving classical 'string sign of Kantor' appearance.

- M/E:
  - Transmural Ulceration
  - ↑ risk of perforation
    peritonitis
    fistula formation/Adhesion
  - Granuloma ⊕ in all layers
  - Cryptitis & Crypt abscess

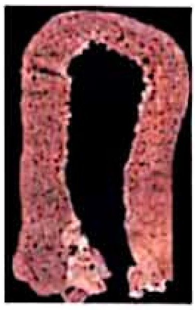
B) ULCERATIVE COLITIS

- Gross :
  - Toxic megacolon
  -
    Normal Colon

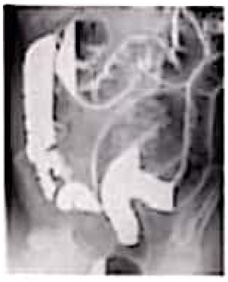
↓ Chronic U.C



Lead pipe deformity
↓
d/t loss of haustration
aka Featureless Colon



ULCERATIVE COLITIS
Mucosa is diffusely red and inflamed. Many inflammatory pseudopolyps are present.



CHRONIC ULCERATIVE COLITIS (LEAD PIPE APPEARANCE)
Double contrast barium enema demonstrates a featureless descending and sigmoid colon, lacking normal haustral marking.

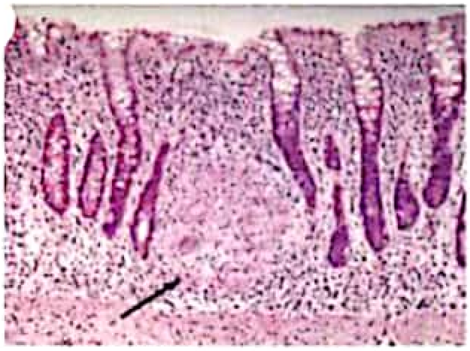
- M/E :
  - Mucosa/Submucosal Ulceration
  - No granuloma
    Eosinophilic & Mast Cell infiltaration ⊕
  - Branching & distortion of crypts
  - Cryptitis & Crypt abscess

Risk : Malignant transformation (CD ≪ UC)

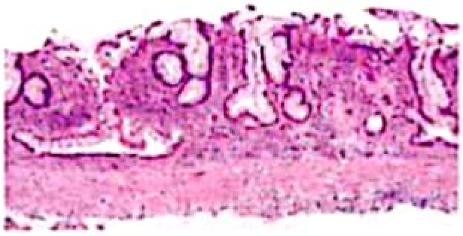
MC C of death : Malignancy > Peritonitis

C/f : Malabsorption ; intermittent bloody mucoid diarrhea

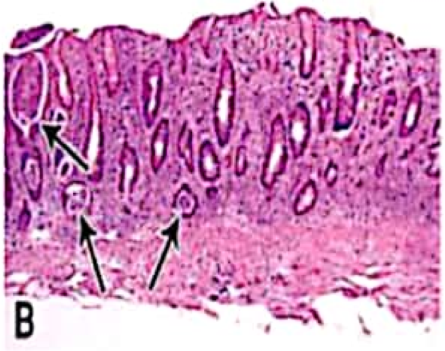
Scanned with CamScanner



CROHNS DISEASE
Biopsy showing noncaseating granuloma formation with lymphoid aggregates in submucosa.



ULCERATIVE COLITIS (UC)
Biopsy showing crypt branching and irregularity of size and shape, with an increase in chronic inflammatory cells in the lamina propria.



ULCERATIVE COLITIS (UC)
A higher-power view of a crypt abscess.

GASTRO INTESTINAL POLYP

- Polyp : mass protruding into the lumen of Gut.
  - TRUE POLYP : all layers are involved.
  - PSEUDO POLYP : only mucosa & sub mucosa involved
- Classification :

Non-neoplastic Polyp

i. Inflammatory Polyp.
  - a/w IBD (UC > CD)
  - aka Pseudopolyps (Mucosa-regenerated)
  - No premalignant risk.

ii. Hyperplastic Polyp

iii. Hemartomatous polyp
  - Eg : a) Juvenile Polyp
    b) Juvenile Polyposis Syndrome
    c) Peutz-jeghers Syndrome
    d) Couden syndrome & Banayan-Ruval caba Riley syndrome
    (These are having common PTEN mutation ∴ also called as PTEN gene mutation polyposis synd)
    e) Cronkhite Canada Syndrome.

Neoplastic Polyp

i. Tubular Adenoma
ii. Villous Adenoma
iii. Tubulo villous Adenoma

Familial Polyposis

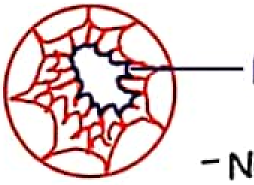
i. Familial Adenomatous Polyposis Syndrome
  - Gardener Synd
  - Turcot Synd.

ii. Hereditary Non-polyposis Colorectal Carcinoma (HNPCC) / Lynch Synd.

HYPERPLASTIC POLYP

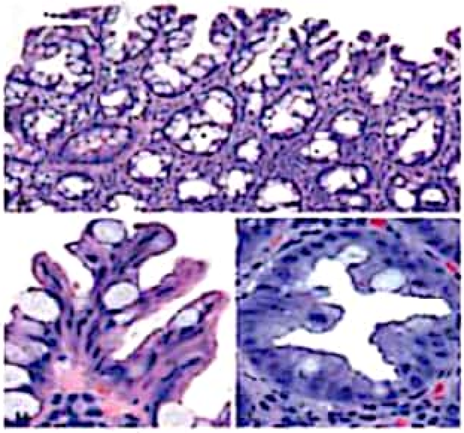
- Seen in Older pt 60-70 yrs
- MC site : Recto sigmoid colon
- Pathogenesis : ↑ proliferation of glandular epi.
  +
  delayed shedding
  ↓
  Overcrowding of gland

- M/E :



Irregular Serrated Surface of Gland (Hallmark)

- No malignant potential



HYPERPLASTIC POLYP
Biopsy showing serrated architecture at the surface without glandular abnormalities.

Scanned with CamScanner

HEMARTOMATOUS POLYP

- a/w mutation in tumor suppressor genes/proto oncogenes
- a/w Intestinal & Extraintestinal Cancer Risk

1. JUVENILE POLYP

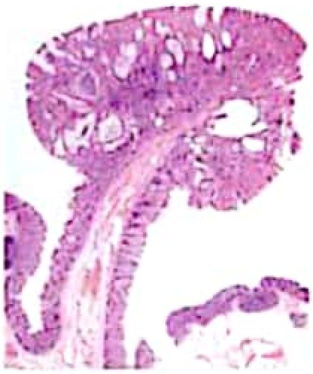
- 5yrs of age group
- MC Site: Rectum
- MC a/w mutation of SMAD-4 gene mutation > BMPA-1

↓

Defective signalling of TGF-β

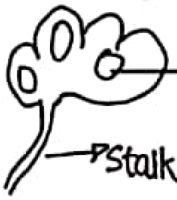
↓

Formation of polyp



JUVENILE POLYP
Microscopy showing cystically dilated glands.

- Gross : Solitary round mass in Rectum
- M/E :

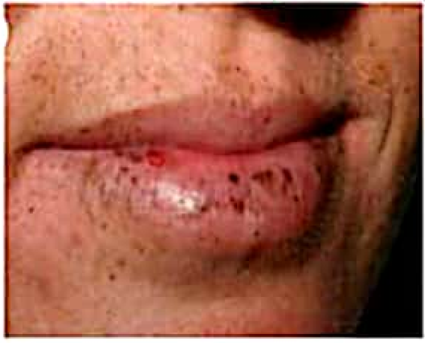


no malignant transformation

2. JUVENILE - POLPOSIS SYND.

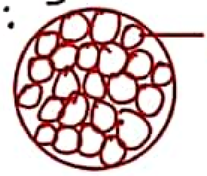
- >100 Hamartomatous Polyp in colon
- Risk :· Ulceration → Bleeding
  ↓
  ∴ require coloctomy
  - Intestinal :
    ↑ Colon adenocarcinoma
  - Extraintestinal :
    Pulmonary arteriovenous malformation

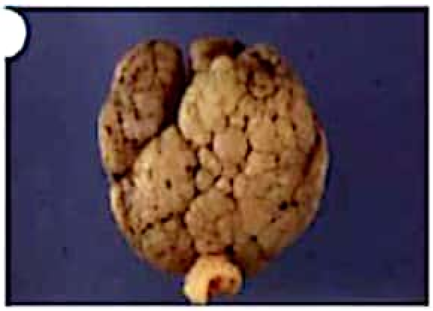
3. PEUTZ - JEGHERS SYND.



PEUTZ-JEGHERS SYNDROME (PJS)
Characteristic presence of perioral mucocutaneous pigmentation

- In pediatric patient (11yrs)
- Pathogenesis : Mutation in LKB-1/STK-11 gene
- C/f : Gastrointestinal Polyp
  +
  Mucocutaneous Hyperpigmentation
  in the form of macules in
  - Perioral
  - Perianal / Genital area
- ↑ Risk of malignant transformation
  - Breast Ca
  - Thyroid
  - Pancreas (Most strongest association)
  - Colon
- Gross :

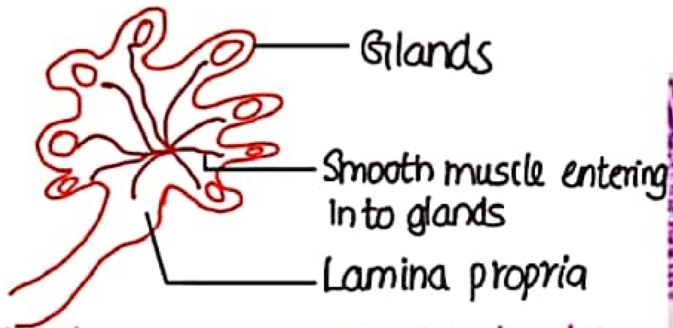


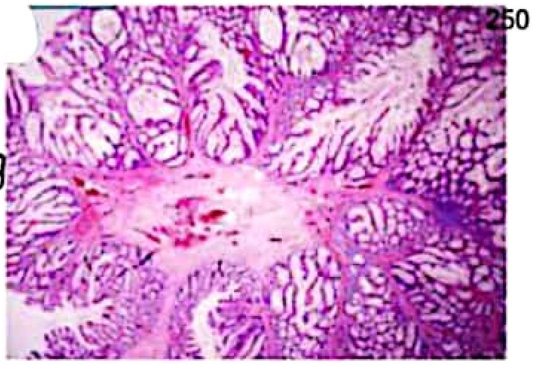


PEUTZ-JEGHERS SYNDROME (PJS)
Bosselated gross appearance.

Scanned with CamScanner

- M/E :





PEUTZ-JEGHERS SYNDROME (PJS)
Peutz-Jeghers polyp shows hyperplastic mucosal epithelium and arborizing bands of smooth muscle, consistent with a hamartomatous polyp

Arborisation of smooth muscle, glandular epithelium & connective tissue

smooth muscles intersecting within hyperplastic glandular epithelium

4. COWDEN SYND. & BANAYAN RUVALCABA RILEY SYN.

- aka PTEN Hamartomatous Tumor syndrome

- COWDEN SYNDROME	BANAYAN RUVALCABA RILEY SYN.
↓	↓
i) GI Polyp	i) GI Polyp
ii) Macrocephaly	ii) Macrocephaly
iii) Benign skin tumor	iii) Benign skin tumor
	iv) Mental Retradation &
	v) Developmental anomaly
# ↑ risk of malignancy in	# ↓ risk of malignancy in
• Breast	• Breast
• Thyroid	• Thyroid
• Endometrium	• Endometrium

5. CRONKHITE CANADA SYNDROME

- Non hereditary condion
- >50yrs old
- C/f : GI Polyp + Hair loss + Skin pigmentation altered + Nail-atrophy

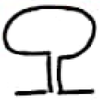
Cachexia even if we give t/t
↳ a/w >50% of mortality

NEOPLASTIC POLYPS

- MC Neoplastic polyp : Adenoma → Charachteristic Histological finding } DYSPLASIA

1. TUBULAR ADENOMA

- MC type of adenoma
- MC Site : Sigmoid colon
- Gross : mushroom like glandular proliferation with stalk



2. VILLOUS ADENOMA

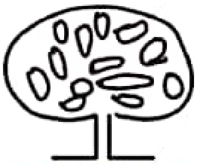
- max malignant transformation
- MC Site : Sigmoid colon
- Gross : No stalk

3. TUBULOVILLOUS ADE.

- MC Site : Sigmoid colon
- Mixture of Tubules + Figarlike projections.

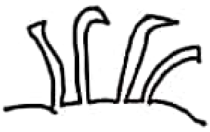
Scanned with CamScanner

-MIE :

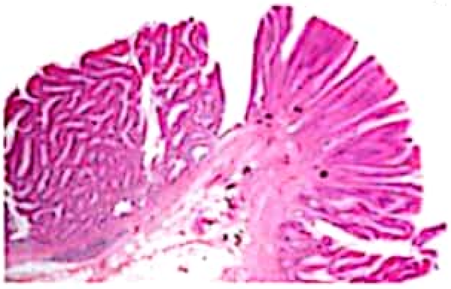


Complex branching of glands (tubular)

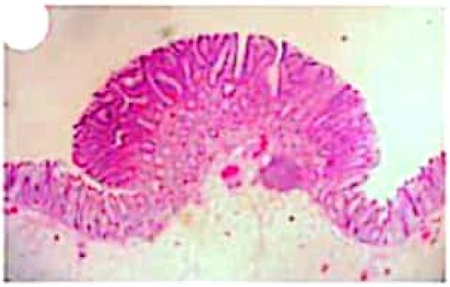
-MIE :



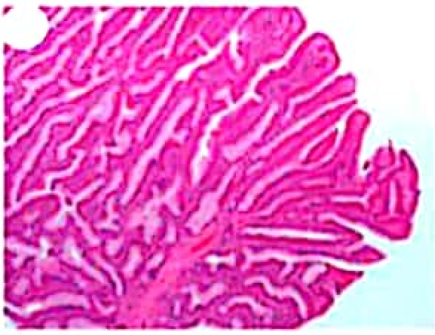
Slender fingerlike arrangement of glands



TUBULOVILLOUS ADENOMA
showing mixture a villous morphology and tubular morphology.



TUBULAR ADENOMA
showing complex branching of glands



VILLOUS ADENOMA
shows many slender, finger-like villi.

FAMILIAL POLYPOSIS SYNDROME : Autosomal Dominant inheritence

I. Familial Adenomatous Polyposis

- AD d/t mutation of APC gene
- >100 Colonic polyps present.

100% risk of cancer transformation within 30yrs

- 2 variants

Gartner Syndrome
Desmoid tumors
Dentition problems
Multiple osteomas
↑ risk of · duodenal
· Thyroid cancer

Turcot syndrome
#Colonic polyp
+
CNS Tumor
(Medulloblastoma)

II Hereditary Non Polyposis Colonic Cancer

- aka Lynch Syndrome
- d/t Mismatch repair gene mutation
↓
microsatellite Instability

- ↑ risk of extraintestinal tumor
→ Breast Ca
⇒ Endometrial Ca.

INTESTINAL TUMORS

- MC intestinal Tumor : Benign → Adenoma
Malignancy → Adenocarcinoma of intestine
more commoner than Carcinoid

INTESTINAL ADENO CARCINOMA

- Male>F : 40-70 yrs

Scanned with CamScanner

- C/f :
  - Abdominal discomfort
  - Abdominal pain
  - Mass causing obstruction
  - Malena
- Risk factors :

Increase Risk	Decrease Risk
Smoking	High fiber diet
Alcohol	Omega Fatty acid (fish)
Nitrites	
Smoked & salted food	NSAIDS
	Estrogen
Low dietry fibers	
IBD(UC>CD)	

- Pathogenesis : APC β-catenin pathway defect
  - APC gene is a negative regulator of β-catenin (normal condition)
  - Mutation → ↑ β-catenin

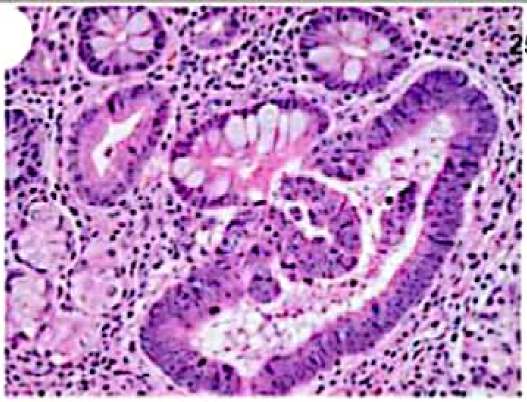
↓

Nucleus

↓

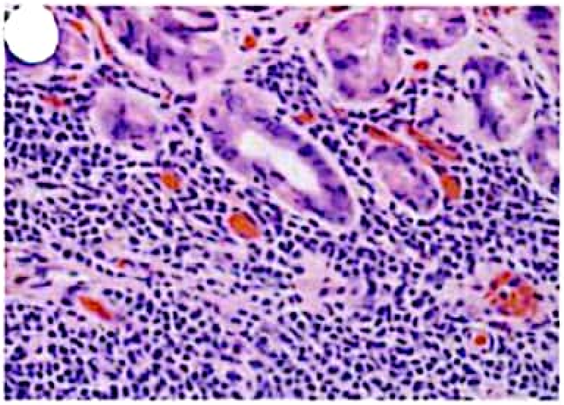
↑Nuclear Transcription Factor (Carcinogenesis)

- a/w p53 mutation
- a/w Microsatellite Instability



INTESTINAL ADENOCARCINOMA

Microscopically, there are innumerable poorly formed glands replacing mucosa in this intestinal-adenocarcinoma

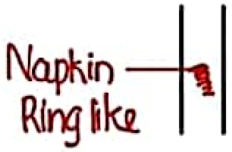


INTESTINAL ADENOCARCINOMA

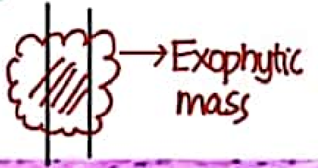
Microscopically, there are innumerable poorly formed glands replacing mucosa in this intestinal-adenocarcinoma

- Gross :

Left side colon



Right Side Colon



- M/E :

Tall coloumnar abnormal tumor forming intestinal cell

Signet Cells are also seen.

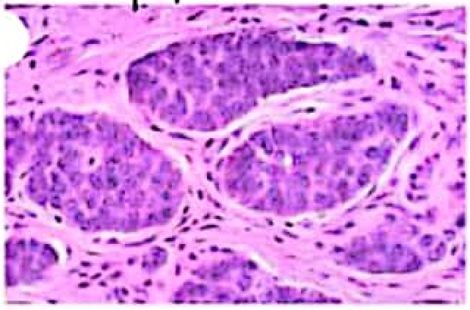
#MC site for metastases : Liver

CARCINOID TUMOR

- neuroendocrine tumor
- MC Site : GIT>Lung
- MC Site in GIT:
  Appendix >Ileum
- C/f : diarrhea
  Constipation
  Abdominal pain
- Gross : Well circumscribed brown tumor mass
  ↓
  d/t Lipofuschin pigment

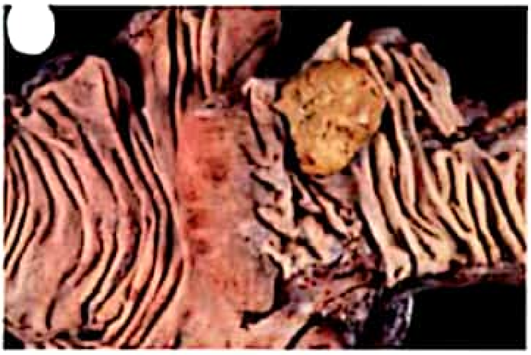
Neuro secretory granules on EM: Dense core granules

- M/E :
  - Round uniform small tumor cell arranged In sheets In b/w fibrous septa
  - Salt pepper chromatin
  - Neurosecretory gran.



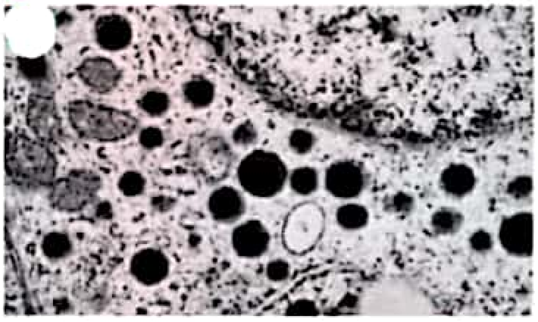
CARCINOID TUMOR

Nests of carcinoid tumor have a typical endocrine appearance with small round cells having small round nuclei and pink to pale blue cytoplasm.



CARCINOID TUMOR

at ileocecal valve is yellowish brown in appearence.



CARCINOID TUMOR showing dense core granules on EM.

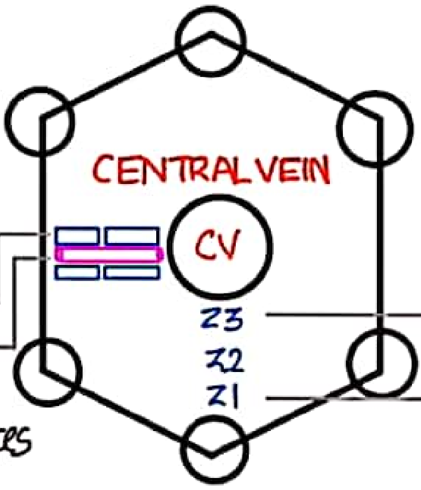
Scanned with CamScanner

LIVER

INTRODUCTION

Weight : 400-600gm

Z3 : PERICENTRAL AREA
Z2 : MID ZONAL AREA
Z1 : PERIPORTAL AREA



PARENCHYMAL PLATE → contain sheets of hepatocytes

SINUSOIDS

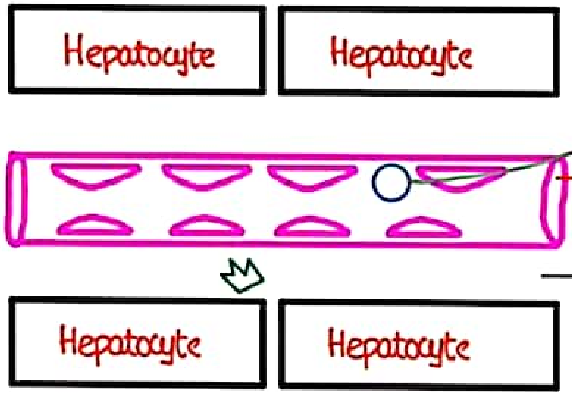
→ PORTAL TRIAD
i) Portal vein
ii) Hepatic artery
iii) Bileduct

Z3 → Blood Supply → 30%

Z1 → Blood Supply → 70%

→ Ischaemia [↓O_2] ⇒ Z3 (m. susceptible)

→ Toxin ⇒ Z1 (m. susceptible)



→ KUPFFER CELLS (Modified Macrophage)

→ SINUSOIDAL CAPPILARIES

→ SPACE OF DISSE (Perisinusoidal space)
↓
contain STELLATE CELLS / ITO CELLS
→ ① Vit A metabolism
② Collagen synthesis
→ CIRRHOSIS (by Type I & III)

PATTERN OF NECROSIS

FOCAL

⇒ Some - lobule necrosis
Among lobules some cells effected
- Councilman - Bodies
  Apoptotic Bodies in viral hepatitis
- Kuppffer cell Hyperplasia & Necr.

ZONAL

⇒ Entire lobule Necrosis

① Pericentral Necrosis (Z3)
  in · CHF
   · CCl_4 Poisoning

② Midzonal Necrosis (Z2)
  in · Yellow fever

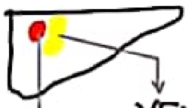
③ Periportal Necrosis (Z1)
  in · Phosphorus poisoning
   · Pre eclampsia & Eclampsia

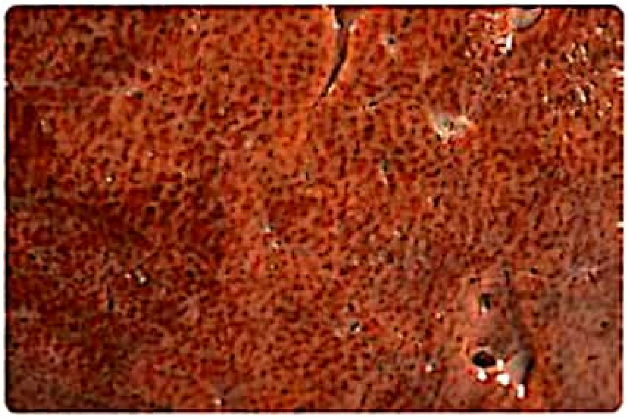
LIVER- INFARCTION

- Rare ∵ dual blood- supply
- Red infarction > White infarction

* Chronic passive congestion (CCPC)

Gross :





Nutmeg liver

NUTMEG LIVER

↓ involve

PERICENTRAL

- Blood supply less
- Ischaemia ⟶ Necrosis (dead cells)

But congestion present

∴ Deadcells + RBC

Dark Red

PERIPORTAL

Cells are viable

YELLOW/TAN

HEPATITIS

ETIOLOGIC

- Viral
- AutoImmune
- Drug induced Hepatitis

HISTOPATHOLOGY

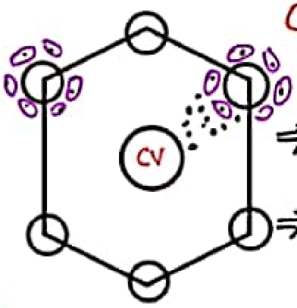
Chronic Persistent Hepatitis

⇒ inflammation limited to limitting plate

limitting plate intact

↓

Single layer of hepatocyte around portal triad



Chronic Active Hepatitis

⇒ Limitting plate is damaged

⇒ inflammation proceeds towards C.V

GRADING

⇒ Based on Necrosis & Inflammation

1. Portal inflammation
2. Periportal inflammation
3. Bridging Necrosis

STAGING

⇒ b/o Fibrosis

G_0 → No Fibrosis

G_1 → Portal Fibrosis/ Mild Fibrosis

G_2 → Moderate / Periportal Fibrosis

G_3 → Bridging/ Severe Fibrosis

G_4 → Cirrhosis

Scanned with CamScanner

HEPATITIS

Based on duration

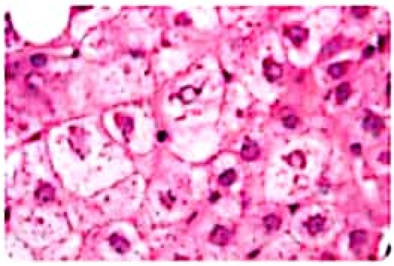
ACUTE

① Ballooning Degeneration

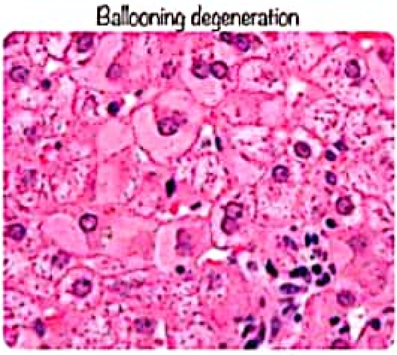
② Councill man Bodies

③ Bridging Necrosis

④ Lobular Architecture preserved



Ballooning degeneration



Ground glass gelato gets

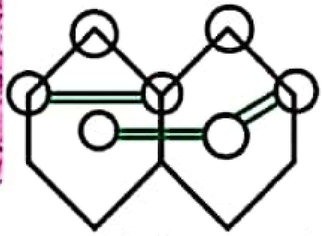
CHRONIC

① Ground Glass hepatocyte

→ Hazy/granular Cytoplasm

due to HBs Ag

② Bridging Necrosis & Fibrosis



1. Portal to Portal
2. CV-CV
3. CV to P

Lobular architecture lost.

③ PIECEMEAL NECROSIS

in Chronic Active Hepatitis

inflammatory damage of limitting plate

④ Fatty changes

JAUNDICE

- Yellowish discolouration of skin & sclera

↓

∵ of ↑ billrubin

- Clinical detection of jaundice : Bilirubin >2.5mg/dl

Bilirubins

Total bilirubin = upto 1mg/dl

Direct/Congugated

* Normal upto 0.3mg/dl
* Water soluble

↓

Easy glomerular filtaration

∴ Present in Urine

INDIRECT/Unconjugated

* Normal = 0.3 to 1mg/dl
* water insoluble
* tightly bound to albumin
* NOT having Glomerular filtaration
* lipid soluble ⟶ Associated with Kernicterus

New born baby brain ⟶ +Uncoj. Bilirubin

HYPERBILIRUBINEMIA

DIRECT/Conju

⇒ Direct Bilirubin >50% of total bilirubin

OBSTRUCTIVE JAUNDICE

⇒ Obstruction/damage of bile duct
⇒ ALP >AST & ALT
[from bile duct Epithelium]

⇒ Gallstone
⇒ Cancer of GB/ Pancreas

HEPATITIS

⇒ inflammation present
ALP < AST & ALT
[Liver cell Necrosis Marker]

INDIRECT/Unconj

⇒ Direct bili <20% of T. Bilirubin

⇒ Hemolytic Anemia
⇒ Physiological Jaundice of Neonates
⇒ Breast feeding induced Jaundice

HERIDITARY HYPERBILIRUBINEMIA

Direct /Conjugated

Dubin Jhonson Syndrome

⇒ Autosomal Recessive
⇒ Mut. → Multidrug Resist. Protein 2
⇒ Harmless Clinical course
⇒ Dark/Black pigmented hepatocytes
∵ of epinephrine metabolite

Rotor Syndrome

⇒ AR
⇒ Harmless Clinical Course

Indirect/Unconjugated

① Criggler Najjar-1
⇒ AR
⇒ fatal in neonatal period

② Criggler Najjar-2
⇒ AR
⇒ Harmless clinical course

③ Gilbert Syndrome
⇒ MC Pattern : AD >AR
⇒ Harmless clinical course

LIVER FUNCTION TEST

Liver Synthesis
- Bilirubin
- Prothrombin
- Albumin

Liver Cell integrity
- AST] Surrogate marker of Liver cell nec.
- Most Specific ← ALT
- LDH
  - ↳ Liver cell Tumor marker

Billiary Excretory function
- Serum Alkaline Phosphatase
- Gamma Glutamyl transpeptidase (GGT)
  - → Surrogate marker of Alcoholic Liver disease
  - → Most sensitive marker of CHOLESTASIS
- 5-nucleotidase
  - → Substitute of GGT
  - ⇒ Most specific marker of CHOLESTASIS

Prothrombin Time (PT)

Liver injury
↓
↑ AST/ALT
↓
Sudden fall in AST/ALT
↓ it may be suggestive of
Check PT

- Recovery → PT = Ⓝ, AST/ALT ↓
- (or)
- Fulminant hepatitis → PT ↑, AST/ALT ↓

Serum alkaline phosphatase ↑

- Bone destruction: GGT Ⓝ, 5-Nu Ⓝ, ↑ S.ALP
- Billiary/Liver damage: ↑ GGT, ↑ 5-Nu, ↑ S.ALP

Hepatitis

- Viral: ALT > AST
- Alcoholic Liver disease: ALT < AST

HEPATITIS

HEPATITIS-A

- Single stranded RNA Virus
- I.P = 2-6 weeks
- MC not associated with ICTERIC PHASE
- Spread : Faeco-oral
- NO CARRIER /NO-CHRONICITY

Diagnosis :
- → Serology : IgM Ab in serum
- → Biopsy : Portal & Peri portal inflammation

Scanned with CamScanner

HEPATITIS-B

- Double stranded DNA Virus in Circular pattern
- associated with DANE Particle /AUSTRALIA Ag
- Incubation Period = 2-26 wks /8 weeks
- Mode of transmission : Blood transfusion
  Needle stick
  Sexually transmitted

Diagnosis

Biopsy : ① Panlobular inflammation
② Ground-Glass Hepatocytes
d/t HBs Ag in ER

Serology : HBs Ag → HBe Ag
↓
anti HBc (IgM)
↓
anti HBe

ANTIGEN

① HBs Ag
- Earliest marker of Hep B
- Epidemiological marker
- Present in Both acute & Chronic

CHRONIC : HBs Ag for >6 months

② HBc Ag
- Not detectable in serum

③ HBe Ag
- feature of viral replication (viral load)
- Suggestive of High infectivity

ANTIBODY

① anti-HBs Ag
- Active or Passive immunisation
- indivual protected

② anti-HBs Ag
↓ IgM HBc
* Earliest Marker for Acute infection
* marker for window period

↓ IgG HBc
* previous/ongoing infection

④ anti-HBe
- Non-infective

Zeroconversion :
HBe Ag ⟶ anti-HBe

Viral replication marker
↓ Qualitative
HBe Ag
↓ Quantitative
HBV DNA > HBV DNA Polymerase

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Carriers of Hepatitis B

SIMPLE CARRIERS

HBs Ag ⊕
Anti- HBe
HBV- DNA = Normal

⇒ Late stage of HepB
Less infectious

SUPER CARRIERS

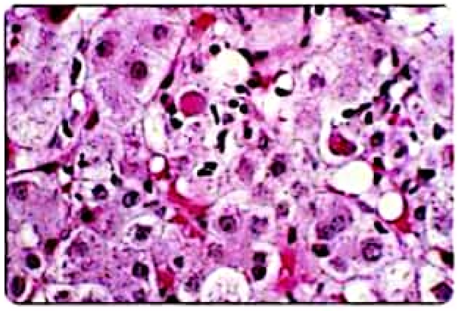
HBs Ag ↑
HBe Ag ↑
HBV-DNA ↑

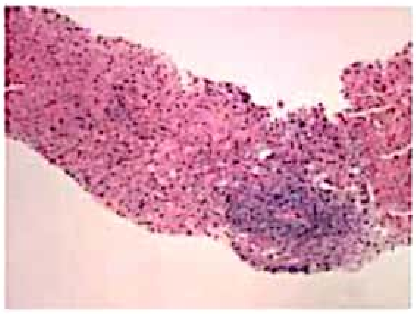
⇒ These are at early stage of infection
They are highly infectious

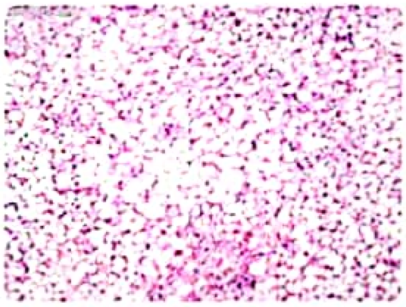
Precore or Basic core Mutant HBV:
- HBe Ag ⊕
- anti HBe ⊕
- HBV-DNA ↑
- Persistent / intermittent AST/ALT ↑
- Suggestive of severe & progressive HBV infection
  Increased risk for Cirrhosis & HCC

HEPATITIS-C

- RNA Virus
- I.P = 4-26 wks (~ 9 weeks)
- Transmission :
  - Blood transfusion
  - Sexually transmitted
  - Intranasal cocaine
- Diagnosis
  - SEROLOGY : IgM / IgG HCV
    BEST METHOD : HCV-RNA on PCR
  - BIOPSY : ① Macrovesicular fatty change
    ② Lymphoid aggregates damaging portal triad
    ③ Councilman Bodies


Councilman bodies


Lymphoid aggregates


Macrovesicular steatosis

HEPATITIS -D

- SSRNA
- I.P = HBV
- Infective when it's coated by HBs Ag

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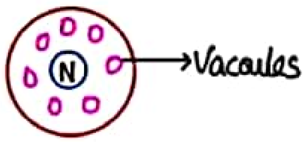
Diagnosis Biopsy : ⇒ Microvesicular Steatosis



⇒ Numerous Councilman bodies

Serology : IgM Ab - anti HDV
HPV-RNA on PCR

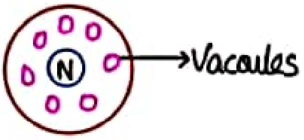
HEPATITIS E

- Rare infection
- RNA virus
- Feco-oral spread
- Maximum Fulminant during Pregnancy

STEATOSIS / FATTY CHANGE

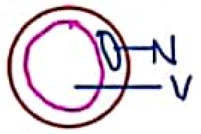
- These are intracellular acculumation of Triglyceride fat within hepatocytes

MACROVESICULAR



⇒ Early stage of alcoholic Liver disease
⇒ fatty liver of pregnancy
Reye-Syndrome
⇒ Drugs : Valproic acid
Tetracycline

MICROVESICULAR



⇒ Late stage of Alcoholic Liver disease
⇒ Diabetes
⇒ Obesity
⇒ Malnutrition (Severe)
⇒ Total parenteral Nutrition
⇒ Phosphorus intoxication

REYE - SYNDROME

- Also known as Jamshedpur fever
- Unknown etiology
- Pediatric patient with Viral illness ± H/O Aspirin injection

- Clinical features : Rash, intra cranial pressure ↑
Vomitting
- Pathogenesis : • Liver mitochondria getting damaged

$$\begin{tikzcd} \text{Liver mitochondria getting damaged} \arrow[d] & & \\ \uparrow NH_3 \arrow[r] & \text{Cerebral Edema } (\uparrow ICP) \arrow[r] & \text{Coma} \end{tikzcd}$$

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- Intracellular accumulation of TG

- Lab investigation : • Hypoglycemia
  • ↑ NH_3

Light microscopy : Microvesicular Steatosis
EM : Mitochondrial damage
↓
Budding & Branching of Mitochondria

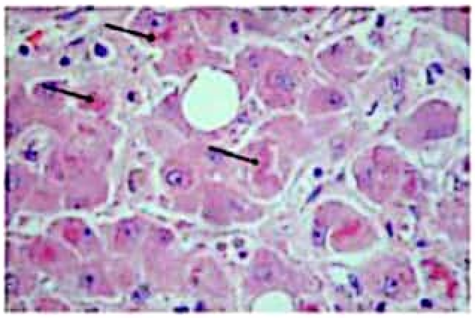
ALCOHOLIC LIVER DISEASE

- Pathogenesis : ↑ Alcohol consumption
  ↓
  FR → I/C accum. fat.
  ↓
  Liver pathology
  ↓ STEATOSIS ↓ STEATO-HEPATITIS ↓ CIRRHOSIS & HCC

STEATOSIS

⇒ intially → Microvesicular
↓
Later → Macrovesicular
⇒ intracellular TG accumulation

Mallory-Denk bodies



STEATO-HEPATITIS

⇒ Steatosis + Slight-Moderate Inflammation

⇒ Mallory Denk Bodies
- Eosinophil cytoplasmic Globular inclusions
- Made up of intermediate filament
  CYTOKERATIN 8/18
- Nonspecific
  Also seen in
  * Wilson disease
  * HCC
  * Primary Billiary Cirrhosis

CIRRHOSIS & HCC

⇒ Pale fibrotic Scar
↓
Replacing entire Liver tissue
aka
Laennec Cirrhosis

⇒ HCC

NON-ALCOHOLIC FATTY LIVER DISEASE -NAFLD

→ No alcohol intake /mild alcohol intake
→ F=M
→ Metabolic Syndrome like : Obesity , TG↑
Diabetes , Insulin Resistance

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→ Microscopy

STEATOSIS

⇒ Both micro & macro vesicular steatosis

STEATO-HEPATITIS

⇒ Nonspecific inflammation with fatty change

CIRRHOSIS & HCC

↑ progression of HCV infection

CIRRHOSIS

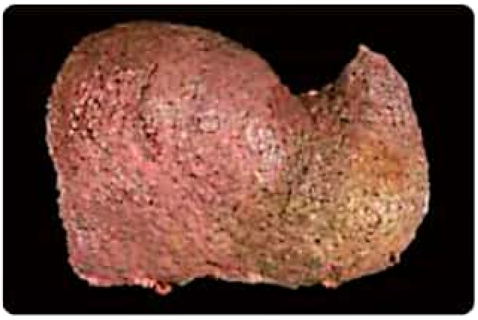
- End stage of chronic Liver disease

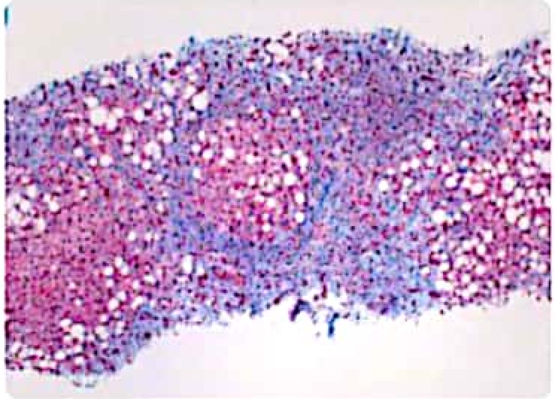
1. Regenerating parenchymal nodules
2. Bridging fibrous septa
3. Loss of Lobular architecture

MICRONODULAR	MACRONODULAR
• Size <3mm	• Size > 3mm
I. Early ALD	I. Late ALD
II. Indian childhood cirrhosis	II. Wilson disease
III. 1° billiary Cirrhosis	III. Viral Hepatitis
IV. Budd-Chiari Syndrome	
V. Hemochromatosis	

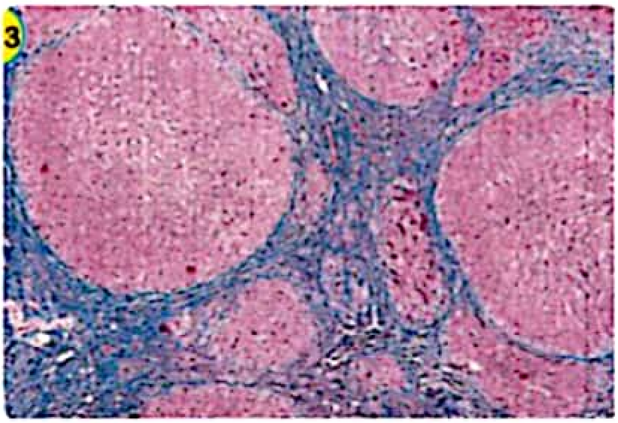
GROSS:

I. Micronodules on surface
No smooth normal surface
↓
Bildman's diagnosis





Micronodular Sclerosis:Mansson trichome stain: stain fibrosis



Macronodular fibrosis: same stain

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NON-CIRRHOTIC PORTAL FIBROSIS (NCPF)

- Young patients 30-40yrs
- M>F
- Etiology :
  - E.Coli
  - Vinyl Chloride exposure
  - Arsenic poisoning
- MC Presentation : Gastrointestinal bleeding
  ↓
  due to rupture of eosophageal varices
- SPLEENOMEGALY + NO JAUDICE + NO CIRRHOSIS + Mild or abesent Ascites + GI Bleeding

[Liver → Ⓝ function]

- BIOPSY : VASCULAR LESION

1. Thrombosis & Sclerosis of portal vein
2. In perisinuscidal areas
   ↓
   Large blood filled spaces
   aka MEGASINUSOIDS formation
   process k/a PERIPORTAL ANGIOMATOSIS
3. Portal & Periportal : Inflammation
   ↓ Cytokine release
   This area Fibrosis also
   NO BRIDGING FIBROSIS
   ↓
   Seen in ALD

WILSON'S DISEASE

- AR
- Mutation in : ATP7-B GENE on Ch13q
  ↓
  ① ↓ billiary excretion of Cu
  ② ↓ combination of Cu with Ceruloplasmin
  ③ inhibit ceruloplasmin secretion in blood
  ↓
  Increased accumulation of Cu^{2+}
  ↓ Hemolytic Anemia
  ↓ Liver disease

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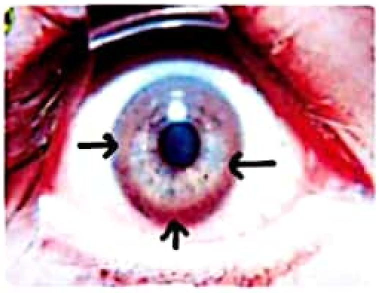
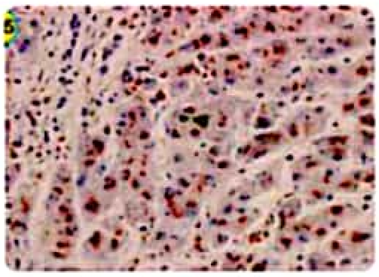
- 6-10yrs (Symptomatic)

Clinical Features

1. Liver (MC)
   - Acute/Chronic/Fulminant Hepatitis (All spectrum)
   - Macronodular cirrhosis
   - Mallory Denk bodies
2. Brain
   - Damage of Basal ganglia
   - Atrophy & cavitation of brain parenchyma especially Putamen
     ↓
     Hepatolenticular Degeneration
   - Association Parkinson Disease
3. Eyes
   - Sunflower cataract
   - Kayser-fleisher rings
     ↓
     In Cornea [Decemet membrane]
     ↓
     Yellow Brown discolouration


Kayser feischer ring

Diagnosis :


Rhodamine staining

- Most specific : ↑ Cu^{2+} excretion in urine
- Gold standard :
  ↓
  Liver biopsy ⇒ ↑ Cu^{2+} [> 250 μg/g of Liv. tissue]
- Rhodamine stain : Red brown colour Cu^{2+}
- ↓ Ceruloplasmin

S. Cu^{2+} level is non-diagnosti (variable)

HEMOCHROMATOSIS

- Iron overload disorder
- AR
- Associated with HFE Gene Mutation on Chr 6p
- TRIAD

1. LIVER (MC)
   - i. Necrosis
   - ii. Micronodular Cirrhosis
   - iii. Risk for HCC
   - iv. No Mallory Denk bodies
2. PANCREAS
   - i. Pancreas damage
   - ii. Diabete Mellitus
3. SKIN
   - i. Bronze Skin
     ↓
     d/t accumulation of Melanin > Hemosiderin

- Also called as Bronze Diabetes

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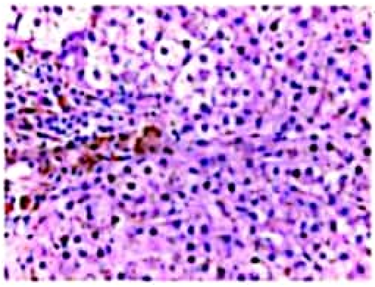
- Infertility (Hypogonadism) in man
  ↓
  Iron deposition in hypothalamo-pituitary
  ↓
  damage
  ↓
  Testicular atrophy

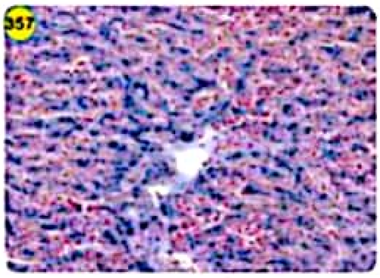


HEMOCHROMATOSIS
Liver biopsy showing hepatocytes with coarse golden yellow granules of hemosiderin within the cytoplasm.

- CVS : Congestive Heart failure
  ↓
  d/t DIALATED CARDIOMYOPATHY > RESTRICTIVE CARDIOMYOPATHY

Diagnosis :

① Micronodular cirrhosis
② brown pigment (Perinuclear)
3 Pearl's Prussian blue staining



Prussian blue

AUTO IMMUNE HEPATITIS

- aka Chronic active hepatitis
- MC autoimmune disorder of Liver
- F > M : 20-50yrs
- a/w inf / drugs / AI disorder
- Classical finding : Only ↑ S.IgG-Abs
  Other markers of viral hepatitis will be normal

Type-1 AI Hepatitis
↓
i. Smooth Muscle Actin Ab (M.Specific)
ii. Anti-nuclear Ab (ANA)(MC)
iii. Liver pancreas / Soluble Liver antigen

Type-2 AI Hepatitis
↓
- Not a/w ANA
- a/w LKM (Liver Kidney Microsomal Ab)

LKM-1 Ab a/w Hep C
LKM-2 a/w DRUGS
LKM-3 a/w HepD

Type-3 AI Hepatitis
↓
- Not a/w ANA or LKM
- a/w Soluble Liver Ag-Ab

- Serology : Raised IgG
- Biopsy :
  * INTERFACE HEPATITIS / PIECE MEAL NECROSIS
  * HEPATIC ROSETTE
  * EMPERIPOLESIS
    Active penetration of in & through the large cell

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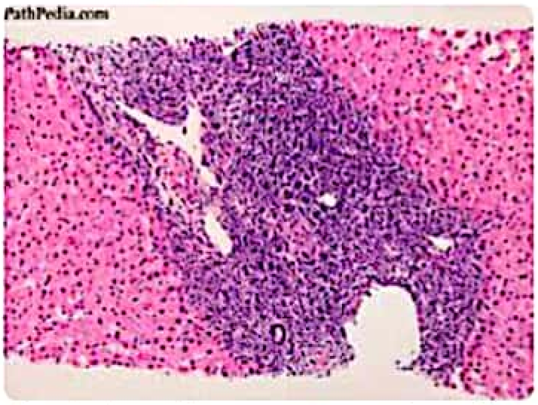
BILIARY CIRRHOSIS

Primary BC

- Autoimmune origin
- MC a/w SCLERODERMA
- F > M , [40-50 yrs]
- C/F:
  - Pruritis
  - Jaundice
  - Hepato spleenomegaly
- Lab Investigation :
  - ↑ Billirubin (conjugated)
  - ↑ S. ALP
- Antibodies : Anti mitochondrial Abs (MC: IgG3)
- Microscopy :
  - * Micronodular Cirrhosis
  - * Granulomatous inflammation causing destruction of bile duct k/a FLORID DUCT LESION

Secondary B.C

- d/t Billiary duct obstruction
  - → In Pediatric
    MC d/t Billiary atresia
  - → In Adults
    MC d/t Gall stones
- C/F:
  - Pruritis
  - Jaundice
  - Hepato spleeno megaly
- Lab Investigation :
  - ↑ Billirubin (conjugated)
  - ↑ S. ALP
- Microscopy
  Bile flakes
  ↓
  causing Bile stasis



Dense lymphocytic infiltration+ granuloma= primary biliary cirrhosis

PRIMARY SCLEROSING CHOLANGITIS

- AI disorder of Liver
- a/w IBD [MC : UC > CD]
- Fibrosing inflammation around both intrahepatic & extrahepatic bile duct.
- C/f : Pruritis
  Jaundice
  Dark-urine
  Hepatospleenomegaly
- Lab finding : ↑ Conj. bilirubin
  Sr. ALP ↑
  ANA
  ANCA (Atypical)
  Rheumatoid Factor
  } Present in serum
- Biopsy : Concentric Fibrosing inflammation
  ↓
  Onion Bulb appearance
- ↑ chance of Cholangiocarcinoma

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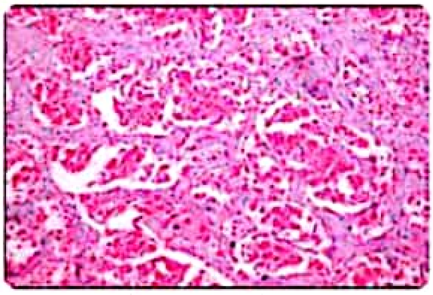
HEPATIC TUMORS

BENIGN : MC Cavernous Hemangioma
Hepatic Adenoma

MALIGNANT : MC Metastasis
(MC 1^0 → COLORECTAL Ca)
MC 1^0 Malignancy :
Hepatoma / HCC

CAVERNOUS HEMANGIOMA

- MC Benign tumor in Pediatric age group
- Dilated vascular channels against the background of fibrous tissue


Cavernous hemangioma

HEPATIC ADENOMA

- Young

# association with OCP rich in Estrogen

- C/F : Abdominal pain
  Intra abdominal haemorrhage
  [d/t ↑ Vascularity]
- On the basis of Molecular pathology

1. HNF-1α

- (Hepatocyte Nu. Factor 1α)
- a/w OCP
- No risk of Malignant transformation

2. WNT-type mutation

$$\boxed{\text{APC} \xrightarrow{\text{degrade}} \text{WNT}}$$

Mutation in WNT
↓
↑ Nu. Transcription factor
↓
Tumorigenesis

- a/w OCP
- ↑ Risk for HCC

3. Inflammation

$$\text{IL-6} \xrightarrow{\oplus} \text{JAK/STAT}$$

- a/w OCP
- ↑ risk for HCC

HEPATOCELLUR CARCINOMA / HEPATOMA

- a/w :
  - Hep B > C
  - ALD
  - NAFLD
  - Cirrhosis → d/t Wilson's disease, → d/t Hemochromatosis, → ALD/NAFLD
  - Aflatoxin (food crop)
    ↓
    Aspergillus inf
  - Tyrosinemia

- Molecular pathogenesis
  - i. WNT activation
  - ii. p53 inactivation
  - iii. IL-6 $\xrightarrow[\oplus]{}$ JAK/STAT

Chronic inflammation
↓
Regenerating nodules
↓
Cirrhosis ⟶ HCC
} HCV/HBV

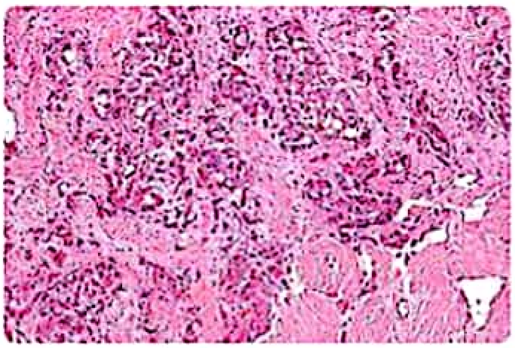
In HBV, have HBX Gene $\xrightarrow{\text{inactivates}}$ p53 within nucleus

∴ it's without Cirrhosis &
>50% asymptomatic

- Tumor markers : AFP
  Hep-par
  Glypican-3
- Microscopy : Adenocarcinoma
  Tumor cells growing in trabeculae

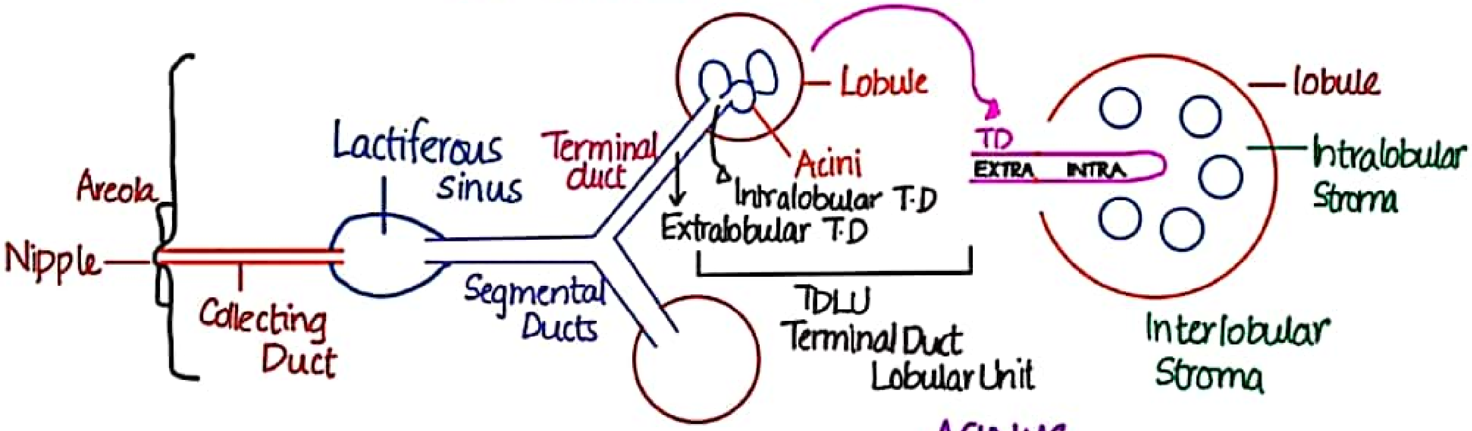
Fibrolamellar HCC :

- F=M
- not a/w HBV or Cirrhosis
- Normal AFP
- Neurotensin is the tumor marker
- Good prognosis

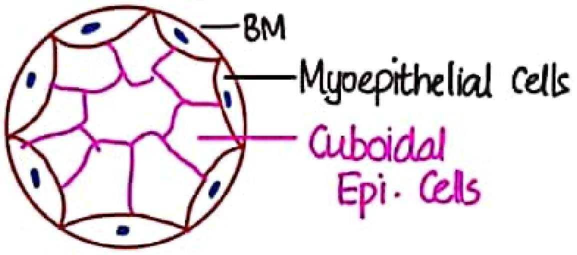


Fibrolamellar variant

BREAST



ACINUS



BREAST PATHOLOGY

Presentation

- Pain
  - CYCLICAL
    - Premenestrual Edema
    - Fibroadenoma
  - NO-CYCLICAL
    - Infections
    - Trauma
- Mass
  - Clinically Palpable mass : >2 cm circumference
- Nipple discharge
  - SEROUS
    - ✱ Cystic ds
  - BLOODY
    - ✱ intraductal papilloma (MC)
  - MILKY
    - ✱ Prolactioma

INFLAMMATORY LESIONS

ACUTE MASTITIS

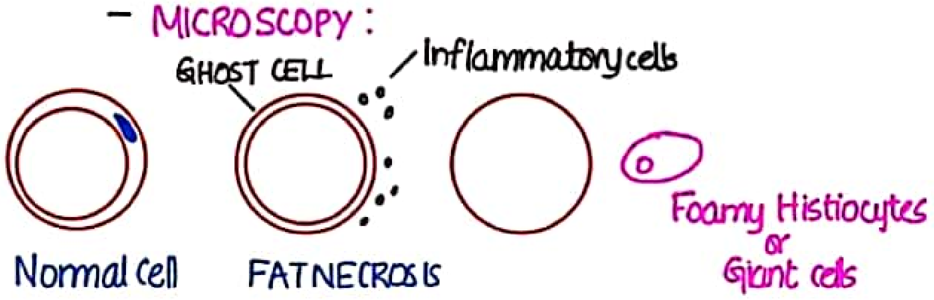
- within Ist month of lactation
- MC due to staphylococcal infection

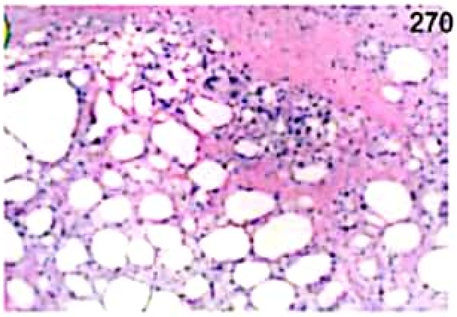
FAT NECROSIS

- D/t trauma / Sx → Mammography : Dense calcification

Scanned with CamScanner

- MICROSCOPY :

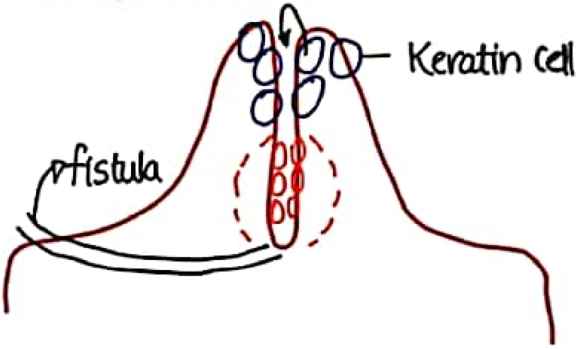




FAT NECROSIS OF BREAST
Showing Foamy histiocytes and occasional multinucleate giant cells surrounding cystic spaces

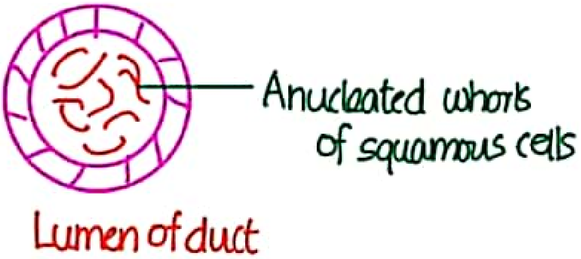
ZUSKA'S DISEASE

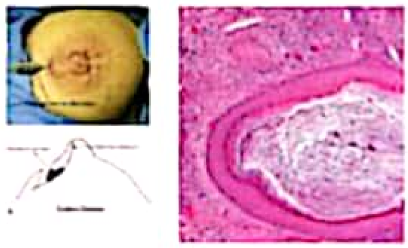
- aka Recurrent Subareolar-abscess
  aka Squamous metaplasia of Lactiferous duct
- MC a/w SMOKING



In Zuska's disease
Keratin cell shed down
↓
Obstruction
↓
Infection
↓
Abscess
↓
Dilatation & Rupture of duct.
↓
formation of fistula

- Microscopy :

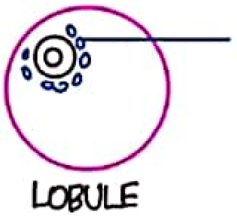




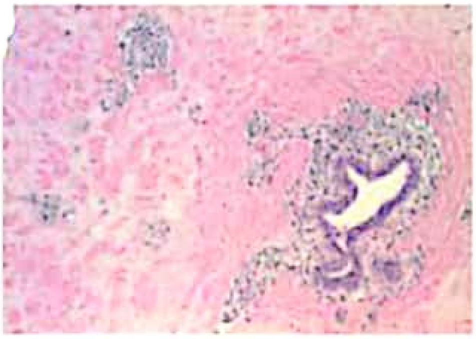
SQUAMOUS METAPLASIA OF LACTIFEROUS DUCTS / RECURRENT SUBAREOLAR ABSCESS/ PERIDUCTAL MASTITIS / ZUSKA DISEASE
Grossly shows Characteristic fistula tract tunnels under the smooth muscle of the nipple and opens onto the skin at the edge of the areola.
Keratin shed from the squamous cells plugs the ductal system, causing dilation and eventually rupture of the duct.

LYMPHOCYTIC MASTOPATHY

- aka Sclerosing Lymphocytic Lobulitis
- a/w Autoimmune disorders : Type-I DM
  aka Diabetic Mastopathy



Lymphocytic infiltarate
↓
Atrophic ducts
⊃ Collagen deposits



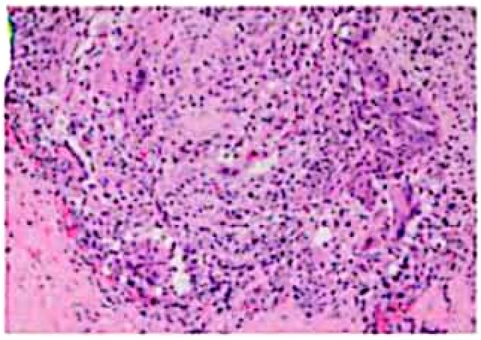
LYMPHOCYTIC MASTOPATHY (SCLEROSING LYMPHOCYTIC LOBULITIS)
Showing Dense collagenized stroma. Atrophic ducts and lobules have
thickened basement membranes and are surrounded by a prominent lymphocytic infiltrate.

Scanned with CamScanner

GRANULOMATOUS MASTITIS

- a/w Granulomatous inflammation
  ↓
  TB or other Chronic Granulomatous disease
- LACTICIFEROUS DUCT DAMAGE

Around the acinus
* Lymphocytic infiltarate
* Multinucleated Giant Cell



GRANULOMATOUS INFLAMMATION
centered on lobules with lymphocytes, plasma cells, epithelioid histiocytes, multinucleated giant cells and neutrophils.

TUMORS OF BREAST

Benign : · MC Fibroadenoma
· Phyllodes tu

Malignant : (i) Non-invasive
· Ductal Ca. Insitu - MC
· Lobular Ca. Insitu
· Pagets Disease

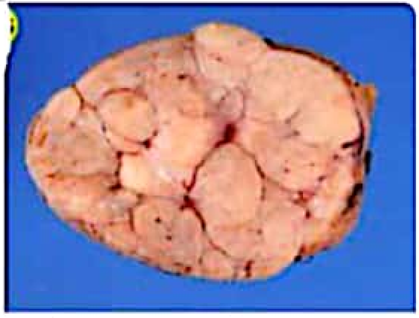
(ii) Invasive Carcinoma
· Invasive Ductal Ca
· Invasive Lobular Ca

I. Tubular
II. Mucinous [Colloid]
III. Medullary
IV. Inflammatory

FIBROADENOMA

- MC Benign tu of breast
- 20-30 yr old patient
- Origin : Intralobular stroma ∴ a Stromal tumor

Gross : - Well circumscribed
- Rubbery
- Glistening white
- Bulging Mass
- Septate spaces



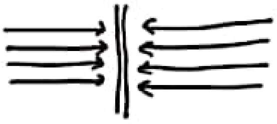
FIBROADENOMA (GROSS)
Cut surface is showing characteristic rubbery, glistening white, well-circumscribed mass and has a septate appearance.

Microscopy : Stromal cells are Neoplastic
Ductal Epi. Cells are Non-neoplastic

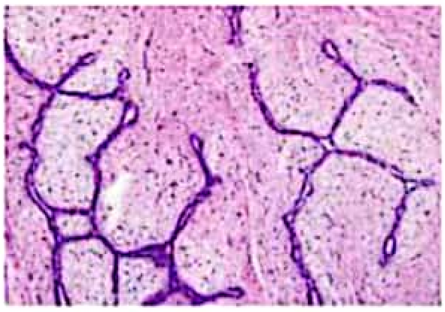
Stromal proliferation ⟶ MYXOID STROMA proliferation (Eosinophilic + Basophilic)

Because of Myxoid Stromal proliferation

INTRACANALICULAR



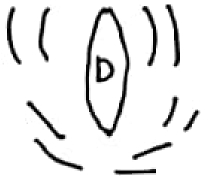
Stromal proliferation compress
the duct epi.



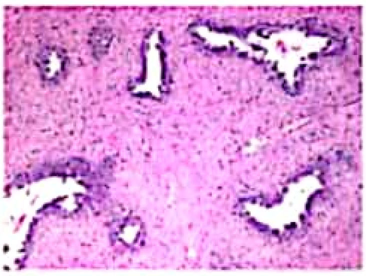
FIBROADENOMA (MICROSCOPY)

It contains a mixture of epithelial and stromal tissue. The stromal component is usually predominant. The epithelial tissue is composed of ducts lined by double layered epithelium and the stromal component is made of fibrous tissue. Based on the growth of the fibrous components, the microscopy is divided into two patterns: Intracanalicular pattern: Fibrous stroma compresses the ducts intc irregular slit like spaces.

PERICANALICULAR



- Duct lumen : Normal
- Surrounded by Stromal Proliferation



FIBROADENOMA (MICROSCOPY)

It contains a mixture of epithelial and stromal tissue. The stromal component is usually predominant. The epithelial tissue is composed of ducts lined by double layered epithelium and the stromal component is made of fibrous tissue. Based on the growth of the fibrous components, the microscopy is divided into two patterns:

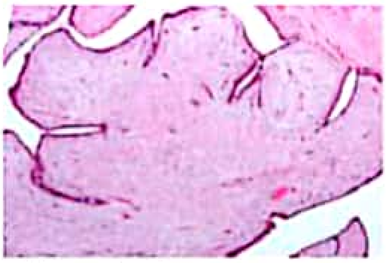
- Clinical Presentation : Painless or painful [∵ of ↑ Estrogen]

Rubbery
Mobile
Breast mass } BREAST MASS

- No malignant potential

PHYLLODES TUMOR

- aka CYSTOSARCOMA Phyllodes
  But no CYST / No. Sarcoma
- Origin : Intralobular stroma
- Benign tumor with Malignant potential
- Not Hormone dependent
- Seen in older patient : 50 yrs +
- CYTOGENETIC Change : MC gain of Cyt. 1
  Over expression of HOX-B13



PHYLLODES TUMORS

They have abundant myxoid cellular stroma separated by long clefts of (compressed) epithelial tissue. The long clefts are the key feature that differentiates these tumours from the more common fibroadenoma of the breast. It may vaguely resemble like leaves (phyllodes = leaf).

Gross : Larger mass

M/E : • Stromal Hyperplasia giving Leaf like appearance
• Stromal Hyperplasia > Epi. Hyperpl.

Scanned with CamScanner

CANCER -BREAST

- MC Cancer seen in females
- Older / Younger
  - → a/w Hereditary Breast Cancers
- Risk factors :

(i) Increases the Risk

- Nulliparity
- Early Menarche
- Late Menopause
- Obesity
- Alcohol
- HRT
- OCP

(ii) Decreases the risk

- Early age of child birth
- Breast beeding
- Caffeine
- Physical exerscise

GENETICS :

BRCA-1

- MC associated
- MC Hereditary Br Ca

Chr. 17q

Female Breast Ca } 1>2
Ovarian Tumor }
Medullary Ca Breast
Metaplastic Ca
Tripple Negative Breast cancer/
Basal Type of Breast ca.

Her 2/neu }
ER } -ve
PR }

BRCA-2

Chr. 13q
MC a/w Male Breast Cancer (2>1)

- Luminal A&B type of Breast cancer

p53

MC a/w Sporadic Breast cancers

CHEK-2

a/w Radiation Exposure associated Breast Ca

MOLECULAR CLASSIFICATION

LUMINAL-A

ER +
PR +
Her-2 -Ve
↓
BEST PROGNOSIS

LUMINAL-B

ER+
PR+
Her-2 +ve
↓
POOR PROGNOSIS

(LUMINAL-A, LUMINAL-B:) BRCA-2 mut.

HER-2

Her-2 +ve
ER -ve
PR -ve
↓
POOR PROGNOSIS

BASAL

Her-2 -ve
ER -ve
PR -ve
= Triple Negative
BRCA-1 mut.
↓
WORST PROGNOSIS

CLAUDIN-LOW

Claudin : Marker of intracellular adhesion
↓ Claudin 3,4,7
↓ exp. E-cadherin
Triple negative
Poor prognosis

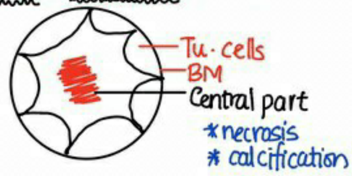
Scanned with CamScanner

Image

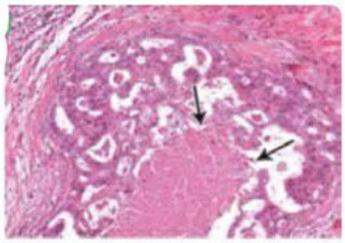
DUCTAL CARCINOMA IN-SITU

- Usually Ca Breast involves TDLU
- Malignant cells are proliferating with in duct without crossing BM.

Comedo Carcinoma :



- No palpable mass clinically
- Mammography → Areas of Calcification

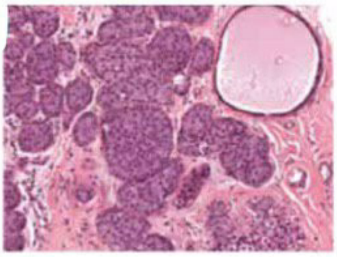


DUCTAL CARCINOMA IN SITU (DCIS) WITH COMEDONECROSIS

Intraductal carcinoma with a cribriform architecture anc central comedonecrosis (arrow).

LOBULAR CARCINOMA IN-SITU

- No mass & No calcification
- Incidental Diagnosis on biopsy
- Malignant tumor cells are in lobules without invading BM.
- No E-Cadherin
  - ↳ ∴ Dycohesive tumor cell ⊕
- Usually Multifocal & Bilateral.

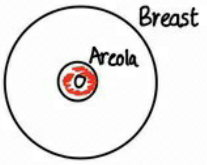


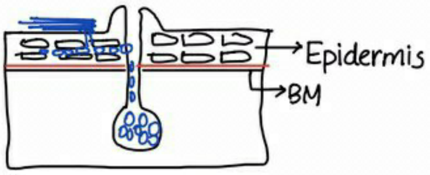
LOBULAR CARCINOMA IN SITU.

The lumina of the terminal duct lobular units are distended by tumor cells, which exhibit round nuclei and small nucleoli. Cytoplasmic mucin vacuoles are present.

PAGET'S DISEASE OF NIPPLE

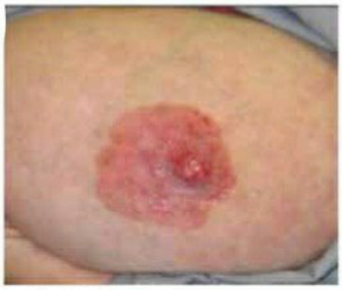
- Rare presentation
- a/w DCIS /or invasive Ca. of breast
- Eczema like erythematous lesion involving nipple c̄ a scaly crust along with pruritis.
- Gross :





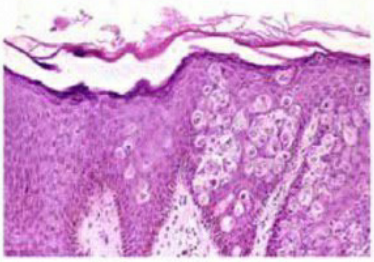
No rupture of BM, Tumor cells are infitarating epithelial cells without rupture of BM

- Microsopy : In epithelium you will see larger cells, Pagetcells
  - * larger cells
  - * Abundunt pale cyto.
  - * Nu c̄ prominent nucleoli
- Molecular analysis : ER /PR -ve Her-2 /Neu ⊕
  - ∴ poorly differentiated & poor prognosis



PAGETS DISEASE

An erythematous, scaly, and weeping "eczema" involves the nipple.



PAGET DISEASE OF THE NIPPLE

The epidermis contains clusters of ductal-type carcinoma cells that are larger and have more abundant pale cytoplasm than surrounding keratinocytes.

INVASIVE BREAST CANCER

INVASIVE DUCTAL CARCINOMA

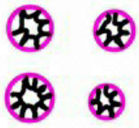
- MC type
- Clinically & Radiologically we can observe tumor

↓ Size >2cm ↓ When size >1cm

- Rupture of BM present

Special Subtypes

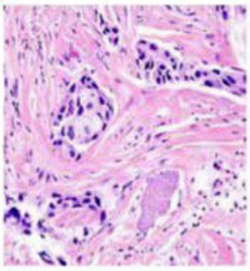
① Tubular



- ER/PR +ve
- Her 2 -ve
- Well differentiated
- Best prognosis

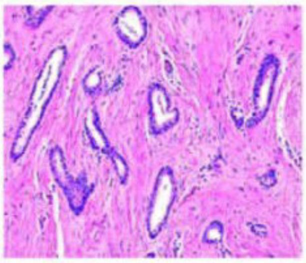
② Medullary Carcinoma

- Mimicking like Fibroadenoma in mammography
- BRCA-1 +ve
- Large tumor cells with
  +
  Prominent nucleoli
  +
  Syncytium-like
  +
  Pushing borders / Infiltarating borders
- Surrounded by Lymphoplasmatic Infiltarate
- Good prognosis



INVASIVE DUCTAL CARCINOMA

irregular cords and nests of invasive ductal carcinoma cells invading stroma.



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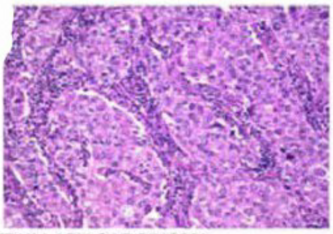


MEDULLARY CARCINOMA

Solid, syncytium-like sheets of large tumor cells with pleomorphic nuclei, and prominent nucleoli, forming a pushing (noninfiltrative) border. There is no gland formation. Numerous mitoses are present. The tumor is surrounded by a dense lymphocytic infiltrate

③ Mucinous / Colloidal

Abundant Mucin present
↓
Tumor cell floats in Mucin

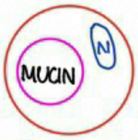
④ Inflammatory

- Clinical appearance like inflammation
  ↓
  ∵ cancer cells are infiltarating dermal lymphatic
  ↓
  Obstruction of Lymphatic
  ↓
  Inflammation & swelling of skin (Breast)
  ↓
  Dense / thick Breast skin c̄ dimpling
  (orange peel)
  Peaud - orange appearance
- WORST PROGNOSIS

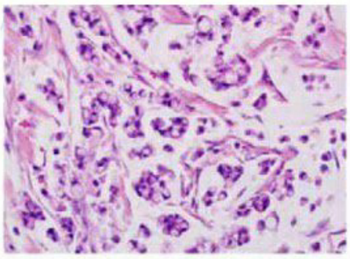
INVASIVE LOBULAR CARCINOMA

- E-Cadherin absent
  ↓
  DYSCOHESIVE Tumor cells
  ↓
  Infiltarate lobule
  ↓
  Tumor cells in Linear fashion
  ∴ Single file pattern
  Indian file patter
- They are multifocal ∴ ↑metastasis
- Also they are bilateral

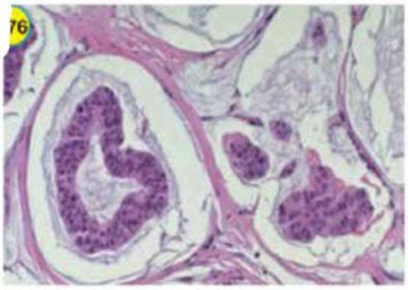
Tumor cells



Signet Ring Cell

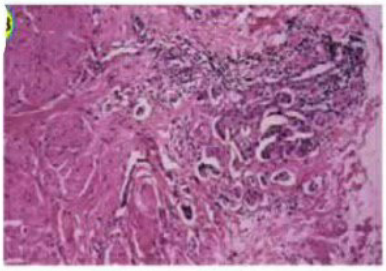


INVASIVE LOBULAR CARCINOMA (SIGNET RING CARCINOMA)
The tumor cells contain large amounts of clear mucin.

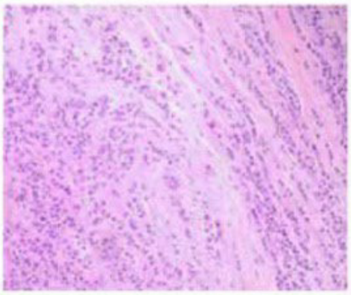


MUCINOUS CARCINOMA
Clusters of malignant cells float in large pools of extracellular mucin.

PEAU D'ORANGE BREAST DUE TO LYMPHEDEMA
It is a swelling occurring as a consequence of a blockage of the lymph vessels.



INFLAMMATORY CARCINOMA
tumors show extensive invasion and proliferation within lymphatic channels, causing swelling that mimics non-neoplastic inflammatory lesions.



INVASIVE LOBULAR CARCINOMA
Lobular carcinoma cells are forming single strands (Indian file pattern) that invade between collagen fibers in a diffuse pattern

PROGNOSIS OF BREAST CARCINOMA

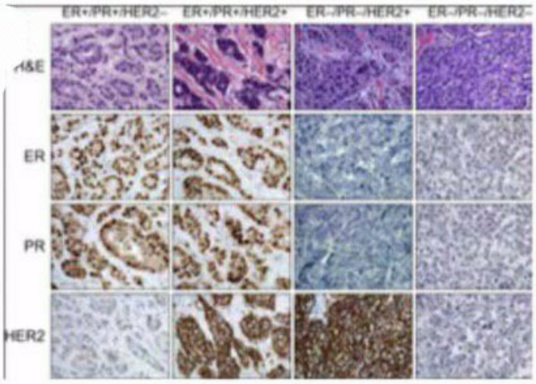
- Ca. In Situ : good prognosis [v/s Inv. Br. Ca]
- NO METASTASES
  - → Axillary LN Status
- METASTASES

ER +
PR + } Good

Her 2 over expression
↓
Bad prognosis

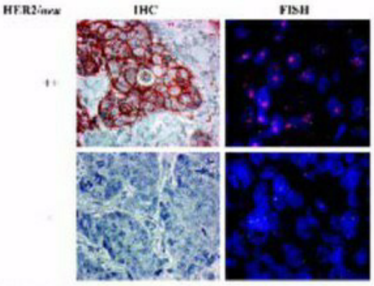
[Worst prognosis : inflammatory Ca
Breast prognosis : Carcinoma in-situ]

[Tripple Negative : Worst prognosis
Luminal -A : Best prognosis]



MOLECULAR SUBTYPES OF INVASIVE BREAST CANCER

On the basis of expression of ER, PR, and HER2.



HER2/NEU EXPRESSION AND AMPLIFICATION

HER2/neu expression and amplification detected by immunohistochemical staining (IHC) and fluorescence in situ hybridization (FISH), respectively.
IHC negative (–) is related to FISH nonamplified (–).
IHC high positive (++) is correlated to FISH amplified (++).
For the FISH assay, green is chromosome 17 centromere; and red is HER2/neu

MALE GENITALS

PENIS

PHIMOSIS

- Abnormal tight foreskin
  ↓
  with impossible retraction over glans penis
- d/t Congenital
  Infections
- Risk : i) 2° infection
  ii) Cancer of penis

BALANOPOSTHITIS

- Balanitis + Posthitis
  ↓ inf. of glans penis
  ↓ inf. of prepuce
- fungal infection Eg: Candida
- Bacteria Eg: Gonorrhea
- d/t SMEGMA
  → Debris of squamous cells & inflammatory cell.
- Risk : Carcinoma

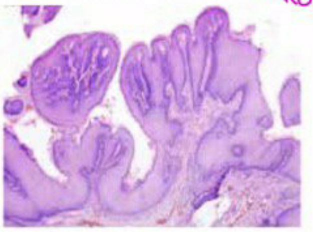
PENILE TUMORS

Benign : Condyloma acuminata

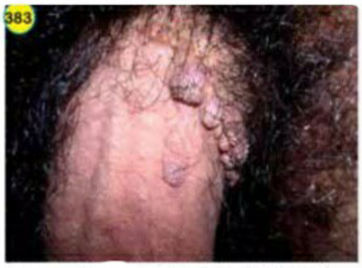
Malignant : Carcinoma in-situ
Invasive sq. cell carcinoma

CONDYLOMA ACUMINATA / Venereal warts

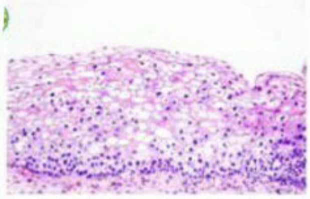
- caused by HPV 6 & 11 infection
- Gross : Sessile
  Pappillary projection
- M/E : - Hyperplastic sq. epithelial cells forming pappill.
  - Koilocytic atypia : Large cell
    Pyknotic nucleus
    Perinuclear halo



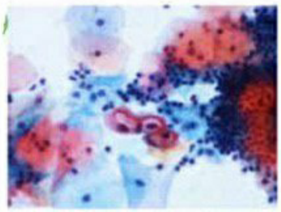
CONDYLOMATA ACUMINATE OF THE PENIS.
Section of a lesion shows epidermal hyperkeratosis, parakeratosis, acanthosis and papillomatosis.



CONDYLOMATA ACUMINATA OF PENIS
These lesions consist of single or multiple sessile or pedunculated, red papillary excrescences



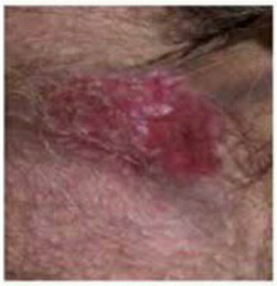
CONDYLOMA ACUMINATUM OF THE PENIS.
The epithelium shows vacuolization (koilocytosis) characteristic of human papillomavirus infection.



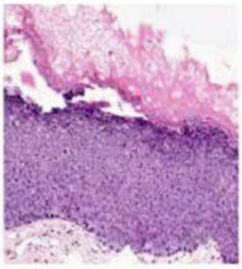
HPV INFECTION WITH KOILOCYTOSIS.
HPV inclusions appear as pyknotic, shrunken nuclei with a clear halo around it (koilocytosis).

CARCINOMA IN-SITU

- Caused by HPV 16(MC) & 18
- M/E : Entire thickness with dysplasia
  BM intact.
- Gross : Red erythematous plaque
  Also known as Bowen's disease
  ↓ ↳ involve carcinoma in-situ of skin
  When it involve Prepuce
  aka Erythroplasia of querat
- Risk : for invasive carcinoma



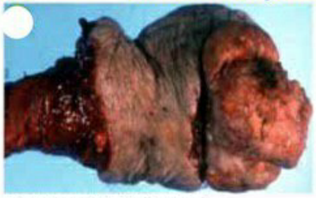
BOWEN'S DISEASE OF THE PENIS
also goes by the name Erythroplasia of Queyrat
a sharply demarcated,erythematous or grayish white plaque on the shaft.



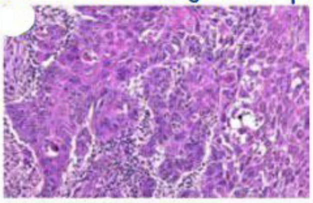
BOWEN'S DISEASE OF THE PENIS
Histologically the epidermis is hyperproliferative, containing numerous mitoses. The cells are markedly dysplastic with large hyperchromatic nuclei and lack of orderly maturation. the dermal-epidermal border is sharply delineated by an intact basement membrane.

INVASIVE CARCINOMA OF PENIS

- The dysplastic cell → Breakdown the BM
  ↓
  Tumor cells will be infiltarating underlying stroma.
- a/w HPV 16 (MC) &18
- Gross : Ulceroproliferative lesion involving shaft of penis
  M/E : Keratinised / Non keratinised Malignant sq. cells



CARCINOMA OF THE PENIS
The glans penis is deformed by a firm, ulcerated, cauliflower like infiltrative mass.



CARCINOMA OF THE PENIS
Malignant squamous cell are infiltrating the tissue.

TESTIS

CRYPTORCHIDISM

- failure of testicular descent into scrotum.
- 2 Components
  - INGUINOSCROTAL
    - Controlled by androgens
  - ABDOMINAL
    - Controlled by Mullerian Inhibiting substances

Not a/w with any hormonal disorders

- MC Site : Inguinal
- Risk : ↑ Risk for Germ Cell Tumor
  Testicular atrophy
- MIE : Hyalinsation & thickening of B.M of Seminiferous Tubule
  No spermatogenesis
  Leydig cells are spared

TESTICULAR INFLAMMATION

- EPIDYDYMIS
  - * Most common
- TESTICULAR
  - * Orchitis

Mumps : -Rare in pediatric age group
-Adults : Parotid infection
↓ 1wks
Testis

TB : - Starting from Epidydymis
Syphilis : - Start from testis

TESTICULAR TUMORS

WHO Classification

- Germ Cell tumor
  - Seminoma
  - Spermatocytic Tumors (= Spermatocytic Seminoma)
  - Non Seminoma
    - Embryonal carcinoma
    - Yolk sac tumor (Endodermal sinus tumor)
    - Teratoma
    - Choriocarcinoma
- Sex Cord Stromal tumors
  - i. Leydig Sertoli cell tumor
  - ii. Gonadoblastoma

GERM CELL TUMOR : MOST COMMONLY MALIGNANT
SEX CORD STROMAL TUMOR: MOST COMMONLY BENIGN

GERM CELL TUMORS

- Most commonly malignant
- Effecting 20-40yrs age group
- MC presentation: Painless testicular mass

Risk factors

i. Cryptorchidism :MC Abdominal type
ii. Testicular dysgenesis Syndrome
    a) Cryptorchidism
    b) Hypospadias
    c) Poor sperm quality
Usually associated with i) Pesticide exposure
ii) Estrogen exposure

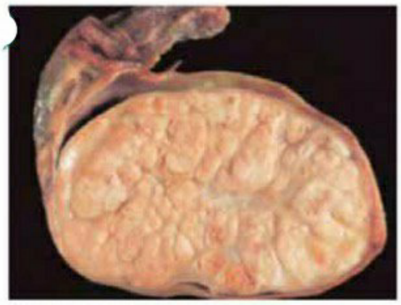
GENETICS :
- C-KIT Mutation
- Transcription factors
  These are also considered as Molecular tumor markers
  i. OCT 3/4
  ii. Nano-G
- i12p (Isochromosome 12p

Seminomas are more common than non-seminomatous
Non seminomatous tumors are MORE AGGRESSIVE, MORE METASTASES
↳ RADIO-RESISTENT
SPERMATOCYTIC TUMORS : BEST PROGNOSIS
↳ RADIO-SENSITIVE ∵ NO METASTASES

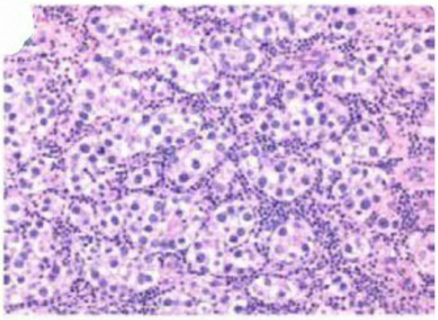
SEMINOMA

- 15-40yrs
- Malignant GCT
- Gross : Well circumscribed
  Encapsulated
  Tumor-bulginging
  Divided by fibrous septa
- M/E : • Tumor cells : • diffuse sheets/nests of tumor cell
  - No glandular pattern
  - Large, Round to polygonal cell
  - Nucleus with prominent nucleoli
  - Cytoplasm may be clear/faded
    ↓
    ∴ of Glycogen
  - Lymphocytic infiltaration in fibrous septa
    Sometimes Granuloma also

for more notes,join our telegram channel, "latest neet pg notes 2020" or join via link " t.me/latestpgnotes"



SEMINOMA OF THE TESTIS
Gross: well-circumscribed fleshy, homogeneous, lobulated bulging tumor replacing most of the body of the testis.



SEMINOMA OF THE TESTIS
Microscopy shows clear seminoma cells divided into dema cated lobules by delicate septa containing large tumor cells with distinct cell borders, pale nuclei, prominent nucleoli, and lymphocytic infiltrate.

Tumor markers for Seminoma : i. Placental Alkaline Phosphatase
ii. LDH (Best)

15% of seminoma arises from Syncitiotrophoblast
↓∴
Secrete β-hcG

Molecular markers : OCT 3/4 / NANO-G
CKIT

SPERMATOCYTIC TUMORS

- Usually >60yrs (older)
- No metastases : ∴ Good prognosis
- M/E : 3 types of tumor cell
  small / medium / Large cell

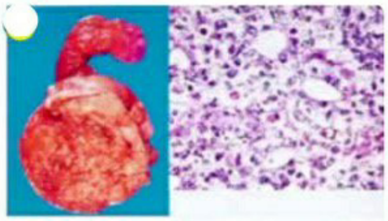
No Granuloma at all
Tumor markers are absent

NONSEMINOMATOUS CONDITIONS

EMBRYONAL CARCINOMA

- Malignant tumor
- 20-30 yrs
- Gross : Mucoid Cyst like tumors
- M/E : Primitive glandular formation

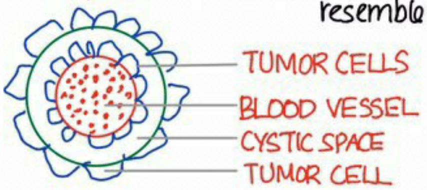
Tumor markers : CK ⊕, C-KIT ⊖
CD30 ⊕
AFP ⊕



EMBRYONAL CARCINOMA IS A HEMORRHAGIC MASS
Embryonal carcinoma shows sheets of undifferentiated cells as well as primitive glandular differentiation. The nuclei are large and hyperchromatic.

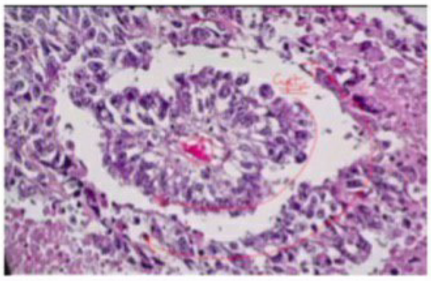
YOLK SAC TUMORS /ENDODERMAL SINUS TUMORS

- Infants & Children
- MC GCT in < 3yr old & infants
- Malignant tumor
- M/E : • Schiller - Duval Bodies
  resemble like primitive glomeruli like appearance



• Central Blood vessel covered by Tumor cells enclosed inside a cystic cavity covered by tumor cell

Tumor markers
i. AFP : Maximum level of AFP ↑
ii. α_1-Antitrypsin



YOLK SAC TUMOR (SCHILLER-DUVAL BODY)

Showing glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space that is also lined by tumor cells (Schiller-Duval body). Tumor Markers are AFP and Alpha-1 antitrypsin.

TERATOMA

- Tumor cell originate from Multiple germ cell layer

i.e Ectodermal : Hair
Mesodermal : Muscles
Endodermal : Thyroid

- Can be matured , immatured , with malignant transformation
  matured ↓ usually benign
  immatured ↓ Malignant ↓ MC a/w Sq. cell carcinoma

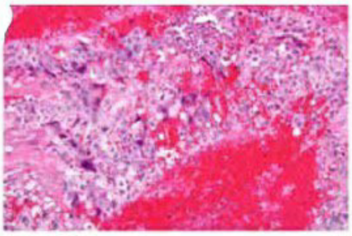
Tumor markers : i. AFP
ii. β-hCG

CHORIOCARCINOMA

Gonadal Chorio carcinoma > Placental Chorio carcinoma
↓
More metastases
↓
↑ Radio resistant
↓
Poorer pro gnosis

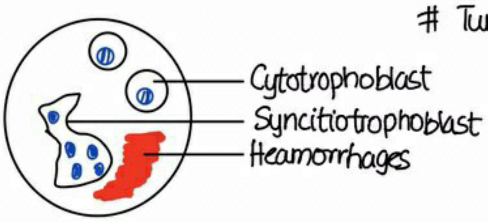
- Malignant transformation

- M/E : Malignant cells composed of
  - i. CYTOTROPHOBLAST : Polygonal cells ̄c clear cytoplasm
  - ii. SYNCITIOTROPHOBLAST : Multinucleated Giant cells



CHORIOCARCINOMA

Shows cytotrophoblastic cells (polygonal cells with clear cytoplasm, bland central nucleus and prominent cell border) and syncytiotrophoblastic cells(multinucleated degenerate-appearing cells with abundant eosinophilic cytoplasm) with areas of Hemorrhage and necrosis.



Tumor marker
i. AFP
ii. β-hcG

ITGCN (Intra Tubular Germ Cell Neoplasia)
→ Carcinoma-in-situ like condition
→ Origin of GCT except : Spermatocytic tumor
Yolk sac tumor
Teratoma

SEX-CORDAL STROMAL TUMORS

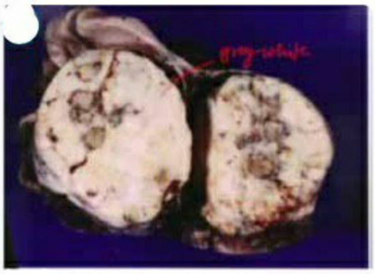
- MC Benign tumors

SERETOLI CELL TUMORS

- >40 yrs age
- presenting with painless testicular mass
- MC : Benign.
- Low quantity of androgen & estrogen formation

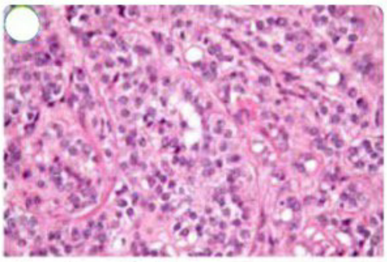
∴ No precocious puberty & Gynecomastia

- GROSS : Grey-white circumscribed mass
- M/E : Tumor cell arrangement in tubular form
  Individual tumor cell : Round to polygonal cell
  Prominent nucleoli
  Cytoplasm with Lipid vacoule



SERTOLI CELL TUMORS

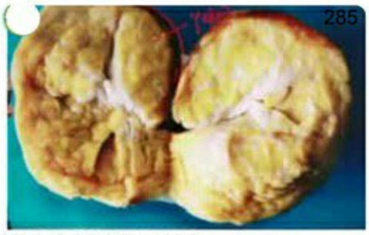
They are small, solid, yellow-gray, well-circumscribed nodules.



SERTOLI CELL TUMORS

tumor cells are arranged in distinctive trabeculae that tend to form cordlike structures and tubules.

LEYDIG CELL TUMOR



LEYDIG CELL TUMORS

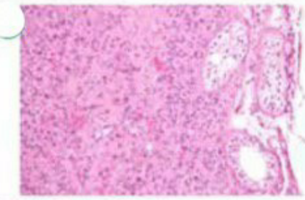
These neoplasms form circumscribed nodules with distinctive golden brown,homogeneous cut surface

- MC Sex cord Stromal Tumors
- 10 - 20 yrs & 30-40 yrs
- MC Benign
- ↑ amount androgen & estrogen

↓

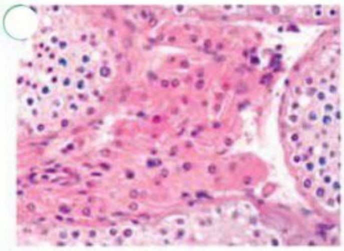
Percocious puberty & Gynacomastia

- Gross : Brown - Yellow mass
  Well circumscribed
- M/E : Solid Sheet pattern : MC Pattern
  Tumor Cells : Round - Polygonal cells
  Granular & eosinophilic cytoplasm
  Reinke Crystal: Eosinophilic intracellular crystals



LEYDIG CELL TUMORS

Neoplastic Leydig cells are large in size and have round or polygonal cell outlines, abundant granular eosinophilic cytoplasm, and a round central nucleus. The cytoplasm frequently contains lipid droplets, vacuoles, or lipofuscin pigment, and, most characteristically, rod-shaped crystalloids of Reinke.



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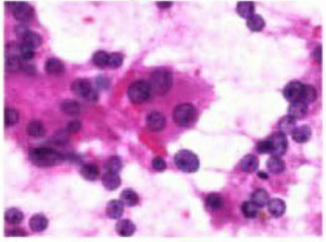

LEYDIG CELL TUMORS

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PROSTATE GLAND

- Growth of prostate is MC controlled by Dihydrotestosterone
- ZONES OF PROSTATE
  - i. PERIPHERAL : MC Site for Prostate Cancer
  - ii. TRANSITIONAL : MC Site for BPH
  - iii. PERIURETHRAL

INFLAMMATION OF PROSTATE : PROSTATITIS

ACUTE

- M/E : Neutrophilic infiltarate
- C/F : • fever
  • dysuria
- Digital Rectal Examination is Contraindicated (∵ Bacterial dissemination)
- MC a/w UTI (E.Coli)

CHRONIC

- Chronic E. Coli
  ↓
  MC a/w E.Coli
- Lymphocytic / Mono nuclear cell infiltaration

Chronic Pelvic Pain Syndrome

- MC Presentation of Prostatitis
- Etiology : Unknown
- Charachteristic Presentation: Increased pain during (or) after ejaculation
- May be a/w inflammation with Leuckocyte in secretion

Granulomatous Prostatis

- a/w BCG - vaccine
- a/w TB infection
- a/w foreign body from Prostatic acini/ duct damage

BENIGN PROSTATE HYPERPLASIA

- Not a pre malignant lesion
- >50 yrs age

Clinical features :
- Lower UT Obstruction
- Dysuria
- difficulty in Stopping & starting urinary stream
- Recurrent UTI

- Pathogenesis : ↑ amount of Dihydrotestosterone

Testosterone

↓ 5α Reductase

Dihydrotestosterone

combine with Androgen Receptor present in the stromal glands

↓

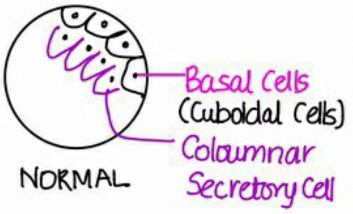
↑ expression of growth factor

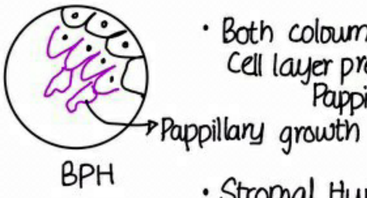
[FGF - 7
TGF - β]

↓

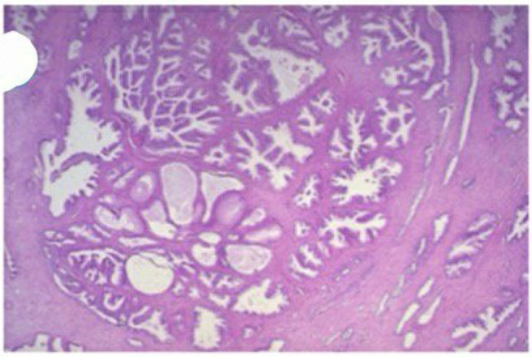
HYPERPLASIA of Stroma & Glands

- Microscopic Examination :



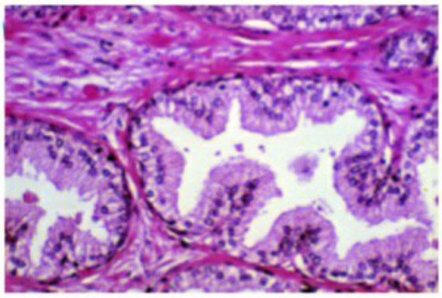


- Both coloumnar & basal Cell layer present with Pappillary Hyperplasia
- Stromal Hyperplasia



BENIGN PROSTATIC HYPERPLASIA

Hyperplasia of glandular and stromal tissue with papillary buds,and infoldings. Basal cell layer is continuous.



BENIGN PROSTATIC HYPERPLASIA

The hyperplastic glands have papillary-like infoldings, with a myoepithelial cell layer (small nuclei near basement membrane). Malignant glands do not have this layer. Note that the stroma divides the glands one from another. Malignant glands are often "back to back", without this intervening stroma.

PROSTATE ADENOCARCINOMA

- Usually seen >70yrs
- MC Asymptomatic /Late symptoms will appear

-Pathogenesis :

DIET
- ↑saturated fat
- Smoking

Decrease Risk by
Lycopene (tomato)
Vit D
Selenium

GENETIC & EPIGENETIC
- BRCA-2 Mutations
- PTEN Gene mutation

ANDROGEN
A+AR
↓
↑Synthesis Nu. T.
↓
Tumarigenesis

Distal Rectal Examination : Stony ,hard ,irregular mass

Radiological Examination : Osteoblastic Secondaries
↓
↑Serum alkaline phosphatase

Diagnosis : • DRE → hard irregular mass
• PROSTATE SPECIFIC ANTIGEN (PSA)
Not specific Prostate adenocarcinama
Also ↑ in • Prostatic infarction
• BPH

PSA level : 4-10 ng/ml → Border line (BPH/Ca.)
10-35 ng/ml → Suggesticve of Cancer
>35ng/ml → Cancer

Microscopic Examination :
- MC Site : Peripheral zone (Post. lobe)
- M.C well differentiated Adenocarcinoma

i. Glandular arrangement
ii. Absence of basal cuboidal epithelial layer
iii. Individual tumor cell Larger
- Larger Nucleus
- Prominent nucleoli (Never seen in BPH)

Perineural invasion is Suggestive of Malignancy

Gleason- System : For grading, staging, & Prognosis
There are 5 pattern
MC pattern + 2nd MC pattern = Gleason score
Minimum ≤6 : Grade-I → Well differentiated
Max : 10 : Grade-V → Poorly differentiated

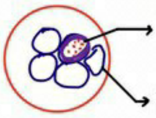
5patterns
i. Cancer cells arranged as small glands
ii. ↑ stromal tissue b/w glands
iii. Distinct infiltaration
iv. Irregular mass of Neoplastic gland
v. No glands are seen

FEMALE GENITALS

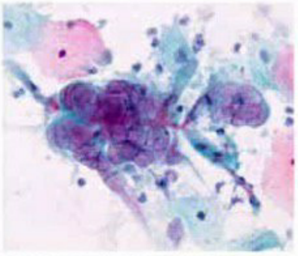
INFECTIONS

1. HERPES SIMPLEX VIRUS (HSV)

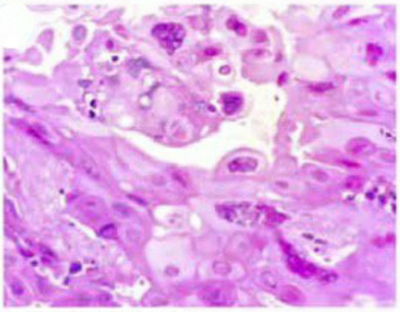
- sexually transmitted disease
- Red papular lesion
- I.P = 3-7 days
- Viruses are latent on nerve ganglia
  ↓
  on Lumbosacral Ganglia
- It require re-activation: done by
  - Stress
  - Immunodeficiency
  - Trauma
  - Hormonal changes
- M/E: → Cowdry A type of viral inclusion within squamous epithelium
  ↓
  both nuclear & cytoplasmic



3 M's
i) Margination of Nuclear chromatin
ii) Multinucleated
iii) Molding of Nuclei



HERPES SIMPLEX INFECTIONS
Infected cells become *multinucleated* and contain *intranuclear viral inclusions* with a characteristic *"ground-glass" appearance*. (Note the 3 "M's"; i.e. Multinucleation, Margination of the chromatin, Molding of the nuclei.)

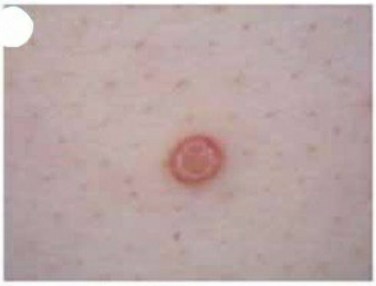


HERPES INFECTION
with diagnostic Cowdry A inclusions and multinucleated cells with nuclear molding and ground glass appearence.

2. MOLLUSCUM CONTANGIOSUM

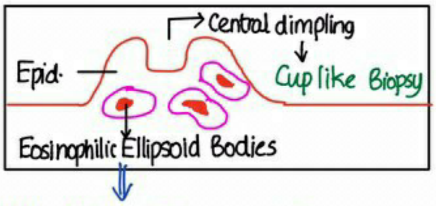
- caused by Pox- Virus
  - Type-1
  - Type-2
    * MC a/w STD
- affect Skin/mucosa
- I.P = 6 wks
- Gross: Pearly papular lesions
  ↓
  - dome shaped
  - central dimpling (d/t the necrotic area)

∴ dome shaped pearly papular lesion with central umblication/dimpling



MOLLUSCUM CONTAGIOSUM
Showing typical flesh-colored, dome shaped or umbilicated papules (dimples in the middle of lesions) and pearly lesions

- M/E :

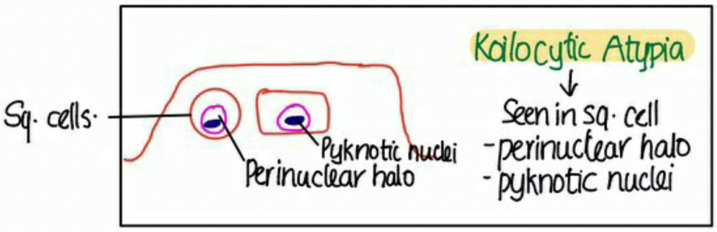


⇓

Henderson- Peterson Bodies

3. CONDYLOMA ACUMINATA

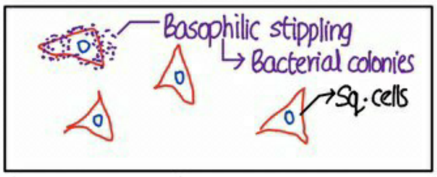
- aka Warts
- Sexually transmitted infection caused by HPV 6 & 11
- Gross examination :
  - Sessile papillary projection
    ⇓
    Verrucous appearance
- M/E :



Koilocytic Atypia
↓
Seen in sq. cell
- perinuclear halo
- pyknotic nuclei

4. BACTERIAL VAGINOSIS

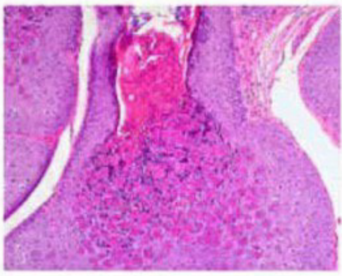
- STD caused by Gardenella vaginalis
- C/f : i) vaginal discharge
  ↓
  thin greenish-greyish in colour
  fishy smell
- Cytology (PAPSmear): Clue cells are diagnostic



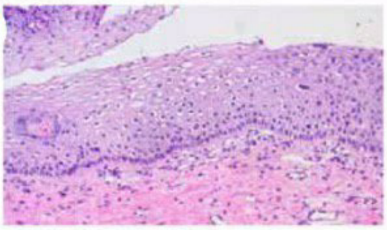
#Basophilic stippling covering entire sq. epithelium
↓
hiding of edges ⇒ Clue cells

5. TRICHOMONAS VAGINALIS

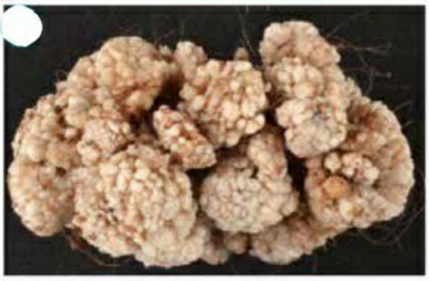
- STD caused by Flagellated Protozoan
- Patient : Asymptomatic or frothy vaginal discharge
- Cytology (PAPSmear) : · Pear shaped organism
  · Elongated nuclei.



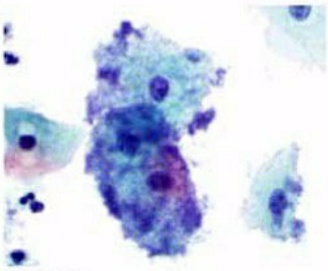
MOLLUSCUM CONTAGIOSUM
Showing cuplike verrucous epidermal hyperplasia with pathognomonic eosinophilic cytoplasmic inclusions known as molluscum bodies (Henderson-Patterson bodies) within stratum granulosum or stratum corneum.



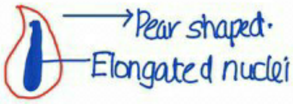
CONDYLOMATA ACUMINATA
Epidermal hyperplasia that is often undulant in character, termed verrucous or papillomatous epidermal hyperplasia, and cytoplasmic vacuolization (koilocytosis) involving the more superficial epidermal layers, producing haloes of pallor surrounding infected nuclei.



CONDYLOMATA ACUMINATA
Lesions shows warty cauliflower-like lesion with papillary or polypoid fronds.



CLUE CELLS
Clue cells are epithelial cells of the vagina. They have distinctive stippled appearance due to bacteria covering epithelial cells. They are sine qua non of bacterial vaginosis. They are a medical sign of bacterial vaginosis caused by Gardnerella vaginalis.



6. ACTINOMYCES INFECTION

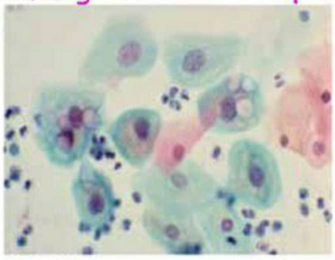
- a/w Intra Uterine Device (Eg: Cu T)
- C/f : • Pelvic pain
  • Vaginal discharge
- Cytology (PAP Smear) :

Actinomycetes (G+ve Bacteria)
↓
Cotton Ball like structure with Radiating filaments (Sun ray like)

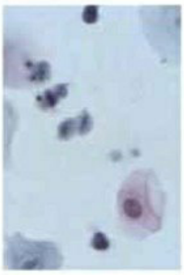
- histopathology : Cotton Ball like with radiating filaments
  ↓
  · necrosis
  · inflammation (Eosinophilic)

7. CHLAMYDIAL INFECTIONS

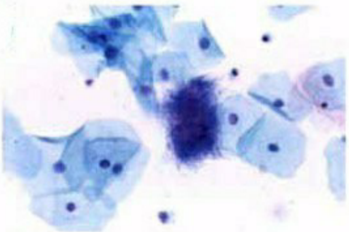
- STD caused by Chlamydia
- C/f : • Vaginal discharge
- Cytology (PAP Smear) :
  Glassy inclusions in Sq. cells.



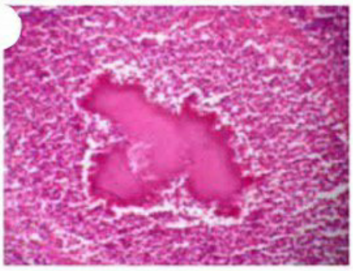
CHLAMYDIA
Chlamydial organisms are large, glassy inclusions containing both reticulate bodies and elementary bodies are clearly visible within squamous epithelial cells.



TRICHOMONAS VAGINALIS
Trichomonas (seen in center of the field) is a pear shaped, oval, or round cyanophillic organism. Nuclei are pale and eccentrically located. Eosinophilic cytoplasmic granules may be visible.



ACTINOMYCES
Colonies of variably gram-positive, long, thin, filamentous bacteria that are reddish or bluish, branch are irregularly beaded, and radiate from central area.



ACTINOMYCES
Colonies of variably gram-positive, long, thin, filamentous bacteria that are reddish, branch are irregularly beaded, and radiate from central area.

VULVR LESIONS

NON NEOPLASTIC

1. LICHEN SCLEROSIS

- auto immune responce seen in postmenopausal females
- Gross : Vulvar skin showing Papules & Macules
  ↓ fuse to
  form thin whitish parchment like skin
- M/E : • Thinning /atrophy of epidermis
- Small risk for sq. cell carcinoma transformation

2. LICHEN SIMPLEX CHRONICUS

- aka Squamous cell hyperplasia
- This is a non-specific responce to chronic rubbing/ itching
- Gross : White plaque like lesions aka Leucoplakia

- M/E : ↑ epidermal thickness d/t sq. cell hyperplasia.
- small risk for Squamous cell carcinoma of vulva

NEOPLASTIC LESION

- MC cancer in vulva : Squamous cell Carcinoma
- 2nd most common cancer : Melanoma

VAGINAL LESIONS

VAGINAL ADENOSIS

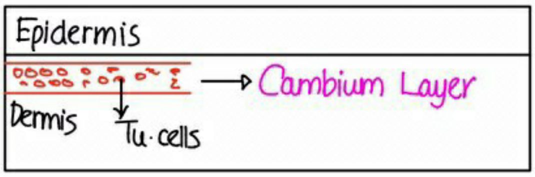
- Seen in females exposed to Diethyl stilbesterol in utero
- On Gross : Red granular patches in vagina
- On M/E : Remenenents of endocervical type of coloumnar epithelium
- ↑ risk for clear cell adenocarcinoma

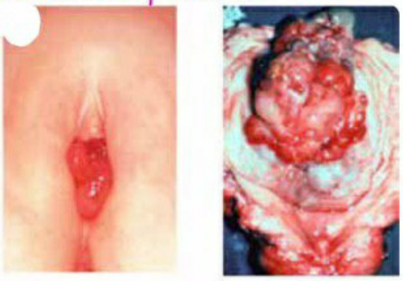
TUMORS OF VAGINA

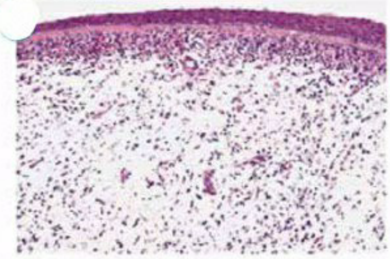
- MC Tumor of vagina : Squamous Cell Cancer

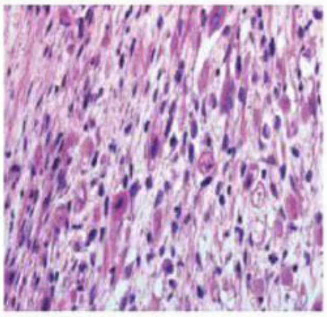
SARCOMA BOTRYOIDES

- Skeletal muscle tumors seen in children (< 5yrs)
- Variant of embryonal Rhabdomyosarcoma involving vagina
- Gross : Vagina → cluster of grape like tumor (Red)
  ↓
  ∴ called as Botryoides
- M/E : Rhabdomyoblast tumor cell
  ↓
  looking like Tennis Racket cells
  ↓
  aka Tadpole cells




SARCOMA BOTRYOIDES
embryonal rhabdomyosarcoma) of the vagina appearing as a polypoid mass protruding from the vagina


SARCOMA BOTRYOIDES
Polypoid or lobulated masses of cells covered by mucosa, with underlying hypercellular zone of poorly differentiated cells (cambium layer).


SARCOMA BOTRYOIDES
(embryonal rhabdomyosarcoma) showing abundant eosinophilic cytoplasm, often with visible cross striations.

CERVICAL LESIONS

CERVICAL INTRAEPITHELIAL NEOPLASIA

- 35 - 40 yrs
- Mostly Asymptomatic (or) post-coital vaginal bleeding

- Risk factors : i. HPV infection
  ii. Smoking
  iii. Immunodeficiency
  iv. Multiple Sexual Partners.
- M/E : Koilocytosis
  - Pyknotic nuclei
  - Perinuclear halo
- In CIN → according to extent of dysplastic cell

- Pathogenesis :

HPV
6, 11 → Benign papilloma
16 (MC), 18 → Cancers

HPV → E6 : ⊖ p53 gene
E7 : ⊖ RB gene

Type - I : Mild dysplasia (dysplastic cells in lower $1/3^{rd}$ of epithelium)
Type - II : Moderate dysplacia (dysplastic cells in $2/3^{rd}$ of epithelium
Type - III : Severe dysplasia (dysplastic cells in $2/3^{rd}$ of epithelium)
Carcinoma-in-situ : Dysplastic cells in entire thickness
BM intact.

UTERUS

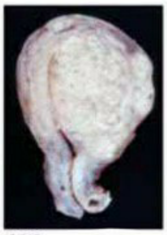
Endometrium inflammation
↓
Endometritis

Acute
- ∗ Bacterial inf. after miscarriage/abortion
- ∗ Neutrophilic infiltarates

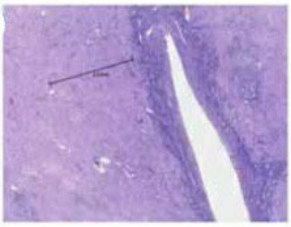
Chronic
- ∗ Secondary to
  - i. PID
  - ii IUD use
  - iii diss. T.B
- ∗ Plasm cell infiltaration diagnostic

ADENOMYOSIS

- Presence of endometrial tissue & glands within myometrium
- C/f : painful irregular meneses
  painful coitus
- M/E : Endometrial tissue present beyond 2-3 mm away from basal layer



ADENOMYOSIS
The cut surface of the uterus reveals small, greyish white areas corresponding to endometrial glands in the myometrium;



ADENOMYOSIS
Showing endometrial gland and stroma within the myometrium

ENDOMETRIOSIS

- ∗ Endometrial tissue outside Uterus
- ∗ MC Site : Ovary
- ∗ M. widely accepted hypothesis
  Retrograde menustruation through fallopian tube
- ∗ C/f : Young, reproductive age
  Dysmenorrhea
  Pelvic pain
  Infertility
- ∗ Endometriotic Tissue v/s Normal Tissue
  - more inflammation
    ↓
    ↑ PG
  - more aromatase activity
    ↓
    (↑ Estrogen)
  - Ovarian Endometriosis
    ↓
    Chocolate Cyst
    (d/t Cyclical bleeding within ovarian tissue)
- ∗ Risk : Endometrial Adenocarcinoma

TUMORS OF ENOMERIUM

1 Malignant Mixed Mullerian Cancer

- aka Carcinosarcoma
- Seen in post - menopausal female
- a/w Radiation exposure
- M/E : Epithelial (glands) + Sarcoma (Spindle cell)

2. ENDOMETRIAL ADENOCARCINOMA

- peak 55-65yrs
- 2 Types

Type - 1	Type-2
* Obesity ↓ ↑ Estrogen	* Thin * Atrophy
* precurssor lesion : Hyperplasia	
* mc a/w PTEN gene mutation	* mc a/w p53 gene mutation
* M/E : resembling like Endometrioid Adenocarcinoma like	* M/E : Serous/ Clear Cell or Mixed Mullerian
* Good prognosis	* poor prognosis

OVARIAN TUMORS

- MC adnexal mass beyond 55yrs of age in females
- Risk Factors :
  - i. Advancing age
  - ii. infertility
  - iii. positive family history
  - iv. Mutation in BRCA1/BRAC2 gene mutation
    BRCA1 > BRCA2
- ↓ses Risk factors :
  - i. OCP
  - ii. Breast feeding
- C/f :
  - MC presentation : Abdominel distention d/t malignant ascites
  - Malignant pleural effussion
  - Obstruction ⟶ Colicky pain
- Tumor markers : CA - 125
  Osteopontin
- WHO Classification

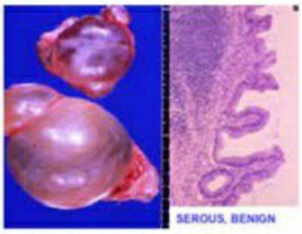
A) Surface Epi. Tum	B) Germ Cell Tum	C) Sex-Cord Stromal	D) Metastatic tum.
MC ovarian Tu.			
i. Serous Tu.	i. Dysgerminoma	i. Granulosa cell Tu.	i. Mullerian
ii. Mucinous Tu.	ii Yolk sac Tu.	ii. Seretoli-Leydig Cell Tu	ii. Extra Mullerian
iii. Clear cell ad Ca.	iii. Teratoma	iii. Thecoma -fibroma	iii. Kruken berg Tu.
iv. Endometrioid	iv Choriocarcinoma	iv. Gonadoblastoma	

- MC ovarian tumor : Surface Epithelium Tumor
  Overall MC ovarian tumor : Serous Cyst adenono carcinoma
- MC Germ Cell Tumor : Dysgerminoma

- MC Sex cord stromal Tumor : Granulosa cell Tumor

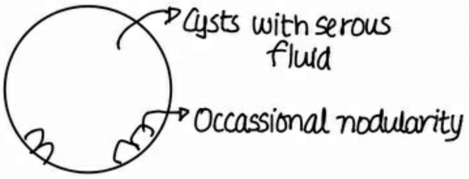
SURFACE EPITHELIAL TUMOR OF OVARY

1. SEROUS TUMORS OF OVARY



SEROUS CYSTADENOMA OF THE OVARY.
A. Gross appearance of serous cystadenoma of the ovary. The fluid has been removed from this huge unilocular serous cystadenoma. The wall is thin and translucent.
B. On microscopic examination, the cyst is lined by a single layer of ciliated tubal-type epithelium.

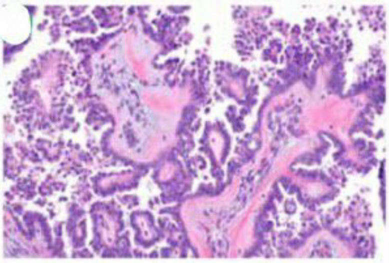
- MC Benign Tu.
- Bilateral
- Gross :



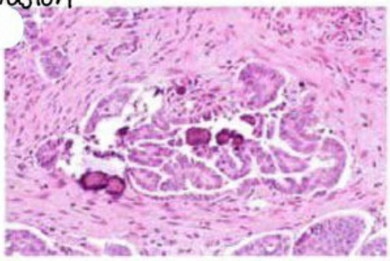
- M/E :

Serous Tumor

Benign Cystadenoma (MC)	Borderline	Malignant (MC Overall)
• Coloumnar epithelium without any invasion	• Mild atypia • Occassional micropapillary projections • No Stromal invasion	• Multilayered coloumnar epithelium • Stromal invasion ⊕

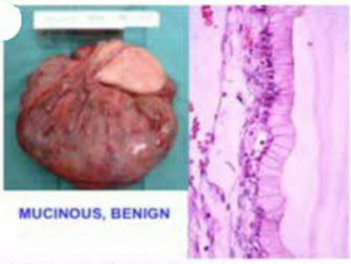


SEROUS CYSTIC BORDERLINE TUMOR.
Microscopic view of the papillary tumor. The papillae show hierarchical and complex branching without stromal invasion. Some papillae have fibroedematous stalks



SEROUS CARCINOMA
The nests of tumor cells are disorderly distributed and appear surrounded by clefts. Also showing the laminated structure of a psammoma body.

2. MUCINOUS TUMORS OF OVARY

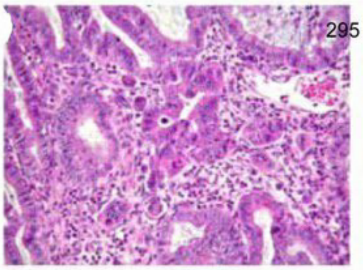


MUCINOUS CYSTADENOMA
Note the multicystic appearance,delicate septa, and the presence of glistening mucin within the cysts.
Microscopy shows Columnar cells lining the cysts

- Unilateral
- MC : Benign
- a/w
  - Smoking
  - K-RAS mutation
- Gross finding : Large multilocculated Cyst filled with Gelatinous sticky mucin
- M/E :

Benign	Borderline	Malignant
• Single layer coloumnar epi. with mucin • No stromal invasion No necrosis	• Atypia • No stromal invasion • No Necrosis	• Multilayered coloumnar • Invasion & Necrosis ⊕

- Charachteristically a/w Pseudomyxoma Peritoneii
  - Peritoneal implantation of Mucinous Tu mass
  - It's MC a/w Mucinous Tumor of appendix

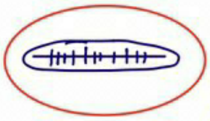


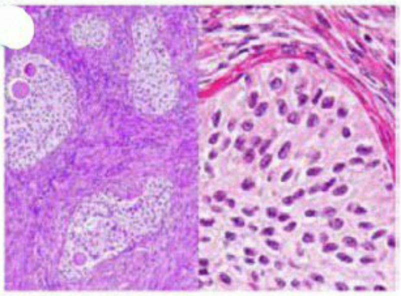
MUCINOUS CYSTADENOMA

The malignant glands are arranged in a cribriform pattern and are composed of mucin-producing columnar cells.

3. BRENNER TU. OF OVARY

- Benign Tumor
- Unilateral
- M/E : i. Watthard Cell nests
  Collection of Tumor cells resembling like Transitional epi. of Urinary Bladder
  ii. Fibrous stroma consist of Watthard cell nest
  Tumor cells with Coffee Bean appearance
  ↓
  d/t Nuclear grooving





BRENNER TUMOR

A nest of transitional like cells is embedded in a dense, fibrous stroma

4. ENDOMETRIOD TUMOR

- These are malignant
- Tu cell resemble like endometrial gland
- Commonly a/w Endometriosis
  Endometrial carcinoma

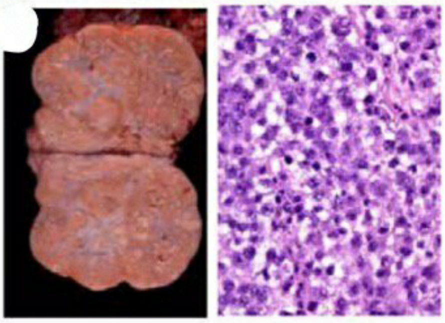
5. CLEAR CELL ADENO CA.

- variant of endometrioid adenocar.
- Rare malignant tumor
- Endometriosis is MC a/w
  Adenocarcinoma of ovary

GERM CELL TUMORS

1. DYSGERMINOMA

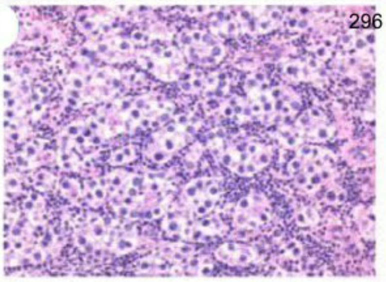
- MC GCT
- Young 20-40yrs
- counterpart of testicular seminoma
- Endocrinologically : Silent tumor
- Gross : • well-circumscribed
  - capsulated
  - Tu cells forming fleshy nodules
  - fibrous septa
- M/E : Same as seminoma
  - Tu cells arranged in nests/cords/sheets
    - → Monomorphic (Round-Polygonal)
    - → Nucleus with prominent Nucleoli
    - → Seperated by fibrous septa
      ↓
      with Lymphocytic infiltarate



DYSGERMINOMA

Neoplastic germ cells are distributed in nests separated by delicate fibrous septa. The stroma contains lymphocytes.

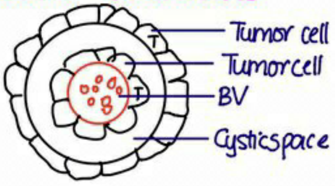
- Tumor markers : • LDH
  - Placental Alkaline Phosphatase (PLAP)
  - Oct 3/4
  - NANO-G



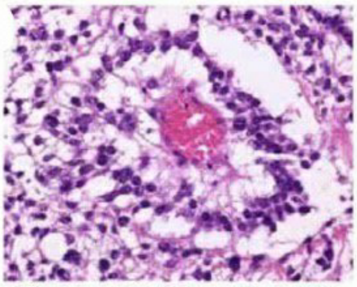
DYSGERMINOMA.
Neoplastic germ cells are distributed in nests separated by delicate fibrous septa. The stroma contains lymphocytes.

2. YOLK-SAC TUMOR

- aka Endodermal Sinus tumor
- Young
- Rare malignancies
- M/E : i. Primitive Glomeruli like structures
  ↓
  aka Schiller-duval Bodies



- Tumor markers : • α-FP
  - α_1-AT

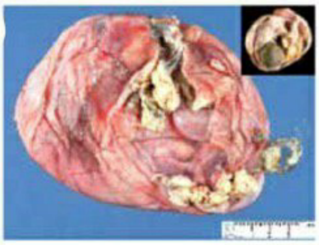


YOLK SAC TUMOR (SCHILLER-DUVAL BODY)
Showing glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space that is also lined by tumor cells (Schiller-Duval body). Tumor Markers are AFP and Alpha-1 antitrypsin.

3. TERATOMA

- Origin : Multiple germ cell layer
- 3 variants

Immature
- Aggressive & Malignant
- Consist of immature cells
  Eg : Muscles/ cartilage
  Bone
- Neuro epithelium ⊕

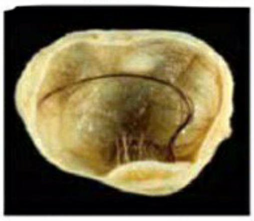


BENIGN CYSTIC TERATOMA
It shows Rokitansky protuberance (arrow).
It contains hair, dermal appendages, bone and teeth arise from these protuberances. Rokitansky protuberance is a common site of malignant transformation. Most common malignant transformation is to squamous cell carcinoma.

Mature / Dermoid
- Consis of Hair + Keratin
- It's always Benign
  in male it's Malignant.
- Cyst with Endo/ecto/ Mesodermal tissue
- Rockitansky protruberance is present
  Protruben consist of
  - Hair, Bone, cartilage
- Clinical Significance :
  Section of this arcas are more prone to Malignant Transformation
  (MC : Sq. Cell Carcinoma)

Monodermal / Specialised
- Differentiation towards single tissue elements
- It's of 2 types
  a) Struma ovarri
    - consist of mature thyroid tissue
    - MC
  b) Ovarian Carcinoid
    - Consist of intestinal carcinoid ⊕

- Tumor cell markers : • β-HCG
  - α-Feto protein



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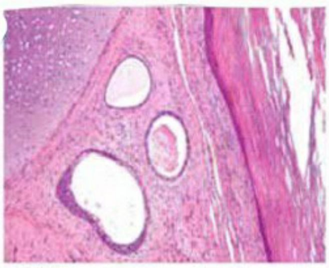
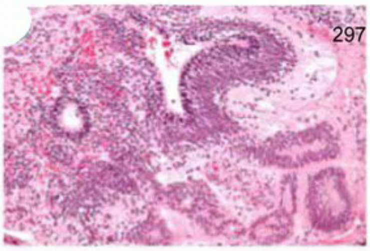
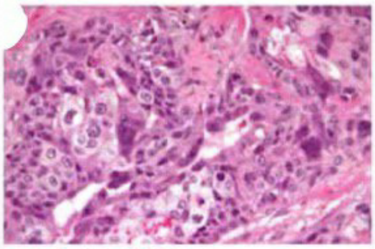


TERATOMA
Testis consisting of a disorganized collection of glands, cartilage, smooth muscle, and immature stroma.



IMMATURE TERATOMA
Tumor shows primitive neuroepithelium of an immature teratoma.

4. CHORIOCARCINOMA



CHORIOCARCINOMA
Shows cytotrophoblastic cells (polygonal cells with clear cytoplasm, bland central nucleus and prominent cell border)and syncytiotrophoblastic cells(multinucleated degenerate-appearing cells with abundant eosinophilic cytoplasm) with areas of Hemorrhage and necrosis.

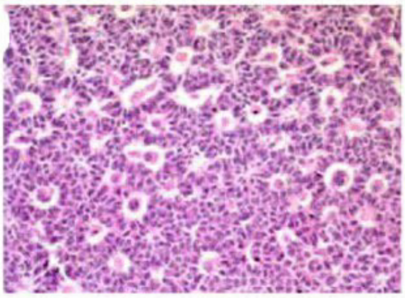
- Origin : Placental (MC) > Gonadal
- M/E :
  - No villi
  - consist of
    - i. Cytotrophoblastic
      Round oval cells with clear cytoplasm
    - ii. Syncytiotrophoblastic
      Multinucleated giant cell

Gonadal Choriocarcinoma :
- More chemoresistent
- Early wide metastases
- Poorer prognosis

- Tumor marker : β-HCG.

SEX-CORD STROMAL TUMORS

1. GRANULOSA CELL TUMOR



GRANULOSA CELL TUMOUR
Histology shows Tumor cells are typically spindle shaped and have a cleaved, elongated nucleus (coffee bean appearance). Call-Exner bodies are seen as a small follicle filled with eosinophilic secretions.

- MC Sex cord stromal tumor of ovary
- Older, post-menopausal. (MC) >50yrs
- Malignant tumors
- ↑ estrogen from tumor cell
  - i) in pre pubertal age → Precocious puberty
  - ii) In Young → Menorrhagia
  - iii) In post-menopausal →
    - PM Bleeding
    - Endometrial Hyperplasia
    - Granulosa Cell tumor
- a/w FOX-L2 gene mutation
- M/E :
  - i. Spindle tumor cells with elongated nuclei
  - ii. Nucleus showing grove : Coffee Bean appearance.
  - iii. Call-exner Bodies
    - These are tumor cell rosette
    - Central part with Eosinophilic secretion
- Tumor markers :
  - i. Inhibin
  - ii. CD99/MIC-1

2. SERTOLI- LEYDIG CELL TUMOR

- aka Androblastoma
- Benign
- Young (30-40yrs)
- ↑androgen ⇒ Virulisation & Hirustism
- Cytogenetics : DICER-1 gene mutation ⊕
- M/E : • Spindle cell tumor cell
  • Leydig cell a/w Rynke crystalloids

3. FIBROMA

- consist of spindle shaped cells
- a/w Meig syndrome
  - i. Ovarian tumor
  - ii Pleural effusion
  - iii. Ascites

METASTATIC TUMOR

MULLERIAN

* arise from Uterus/ Fallopian Tube/ Ovary

* MC : Opposite ovary

EXTRA-MULLERIAN

* arise from Breast
Stomach

KRUKENBERG TUMOR

* MC Primary: Gastric Adenocarcinoma

* Bilateral

* ovarian surface : smooth on gross

* M/E : Signet ring cells.

GESTATIONAL TROPHOBLASTIC DISEASE

- Spectrum of disorders including Tumor & Tumor like lesion
- ↑ trophoblastic proliferation.
- It includes : i. Hydatiform mole
  - ii. Invasive mole
  - iii. Choriocarcinoma
  - iv. Placental site trophoblastic disease.

HYDATIFORM MOLE

- seen in younger 20-40yrs
  older 40-50yrs
- detected during early pregnancy (~9wks)
- Cystic Villi Swelling + Trophoblastic Proliferation
- ↑ risk of choriocarcinoma & invasive mole

HYDATIFORM MOLE

COMPLETE

* empty egg fertilised by one or 2 sperm

* no fetal parts are seen

* genetic materials are paternal origin

* Karyotyping : 46XXY

* More risk of choriocarcinoma

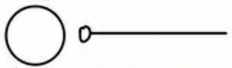
PARTIAL

* formed by egg with Ⓝ Chromosome fertilised by 2 sperms

* Karyotyping : 69 XXX
69 XXY

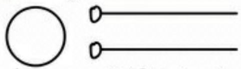
* less risk of choriocarcinoma

- Pathogenesis of Complete mole : 1. Androgenesis (MC)



1ovum + 1sperm (duplicated)

2. Diaspermy



1ovum + 2sperm

- M/E of Complete mole :
  - i. Extensive swelling of villi
  - ii. Extensive trophoblastic proliferation
- Immunostaining : p57 ⊖

- M/E of Partial mole :
  - i. Focal swelling
  - ii. Focal trophoblastic proliferation
- Immunostaining p57 ⊕

INVASIVE MOLE

- Hydropic villi will be infiltarating & perforating myometrium
- ↑ risk of uterine rupture
- high β-HCG.

CHORIOCARCINOMA

- Placental type is MC
- Occur 2° to hydatiform mole (MC)
  - Abortion
  - Pregnancy
- Gross : Mass with Hemorrhagic & necrosis
- M/E : ↑ proliferation of Syncitiotrophoblast & Cytotropho
- β-HCG level is very high
- Risk : Metastases : MC to Lung
- Better prognosis : Chemosensitive

PLACENTAL SITE TROPHOBLASTIC TUMOR

- Increased proliferation of intermediate trophoblast
- No cyto & syncitiotrophoblastic proliferation
- MC a/w Ⓝ Pregnancy
- ↓ level of β- HCG

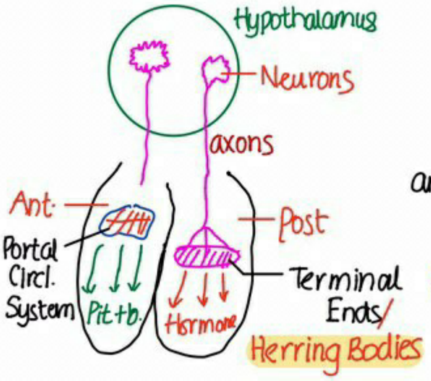
ENDOCRINOLOGY

HYPOTHALAMUS

- Structure present in basal part of forebrain
- contain neurosecretory cells

↓

Control secretion of pitutary hormone



HYPOTHALAMUS
↓
Hormones
↓
Neuronal axon will carry
↓
and transport to pitutary gland

- Anterior lobe → involve portal circulation
- Posterior lobe → involve Herring Bodis

PITUTARY GLAND

- Anterior lobe
  (Adenophysis)
  Portal Circulation
  2 types
  - Acidophilic
    - i) GH Secretors (Somatotrophs)
    - ii) Prolactin Secretors (Lactotrophs)
  - Basophilic
    - i) FSH/LH Secretors (Gonadotrophs)
    - ii) ACTH Secretors (Corticotrophs)
    - iii) TSH Secretors (Thyrotrophs)
- Posterior lobe
  (Neurophysis)
  Herring Bodies
  ⇓
  Storage
  - i) ADH
  - ii) Oxitoxin

PITUTARY GLAND

A) HYPO PITUITARIS M

- * > 75% of pitutary gland destruction
- * MCC of hypopituitarism :
  PITUTARY ADENOMA
- * Earliest hormones effected :
  Growth hormone
- * Causes :
  - i) Surgery
  - ii) Irradiation
  - iii) Sheehan Syndrome
    post-partum pitutary necrosis d/t heamorrhagic shock
  - iv) Empty Sella syndrome
    (d/t pit. destruction)
- * Clinical features
  - i) Growth failure
  - ii) Amenorrhea, infertility
  - iii) Hypothyroidism

B) HYPER PITUITARISM

- * MCC of Hyperpituitarism :
  Pitutary adenoma

↓

Micro adenoma	Macro adenoma
(Size <1cm)	(Size >1cm)
· Usually functional	· Usually non-functional

PITUITARY ADENOMA

- 3 types of Adenoma

A) Prolactinoma

- · MC type
- # Excessive Prolactin hormone secretion
  it's also a/w
  STALK EFFECT
  ↓
  Suprasellar-mass will
  ↓ ⊖
  Hypothalamus
  (inhibit prolactin inhibitory Signals)
  ↓
  ↑ prolactin secretion
- · C/f :
  - i) Galactorrhea
  - ii) Amenorrhea
  - iii) Infertility

B) GH Adenoma

- · Increased secretion of
  - (i) IGF-1
  - (ii) Somatomedin-C

  ↓

  Excessive growth
  Reflected as
- i) Gigantism
  - · Pediatric age
  - · Tall stature
  (Before epiphyseal closure)
- ii) Acromegaly
  - · Adults
  - · Large head, feet, hand mandible
  (After epiphyseal closure)
- # also a/w
  - i) DM
  - ii) HTN
  - iii) Muscle weakness

C) ACTH Adenoma

- · ↑ amount of ACTH
  ↓
  Cushings Disease
- # Nelson syndrome
  - ACTH adenoma
  d/t Adrenal gland Ressection

PITUITARY GLAND TUMORS

A) ADENOMA (MC) ↓ No Metastases

B) CARCINOMA ↓ Metastases present

POST - PITUITARY

A) Oxytoxin

- For milk secretion
  uterine ms. contraction

B) ADH/Vasopressin

- ↑ renal water absorption

Diabetes Insipidus

- ↓ADH → ↓ water absorption
  ↓
  ↑ Na^+ conc.
  (Hypernatremia)
  ↓
  Polydipsia
  Polyuria
- Causes :
  i) Head injury
  ii) Inflammation of brain
  iii) Tumor

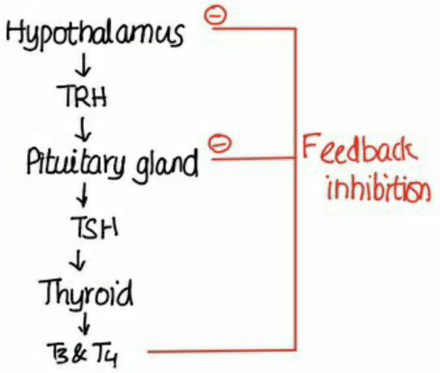
Syndrome of inappropriate ADH Secretion

- ↑ADH → more water reabsorption
  ↓
  Hyponatremia
  ↓
- C/f : Oliguria
  Cerebral Edema
  Neurological deficit.
- a/w Paraneoplastic Syndrome
  MC a/w Small cell cancer of Lung

THYROID GLAND

- Weight : 15-20gms
- 2 types of cells : (i) Follicular cells
  secretion of T_3/T_4 hormone
  help in Ⓝ Brain development
  (ii) Parafollicular cells
  secrete Calcitonin
  help in ↓ Sr. calcitonin

HYPO THYROIDISM



Hypothyroidism

Primary
↓
Thyroid gland affected
↓
- ↓ T_3/T_4 secretion
- ↑ TSH

Secondary
↓
Defect : Pituitary gland or hypothalamus
↓
- ↓TSH
- ↓ T_3 & T_4

- MCC of hypothyroidism : Iodine deficiency
- MCC of hypothyroidism in iodine sufficient area : Autoimmune inflammation
  MC autoimmune inflammation : Hashimoto thyroiditis
- Genetic causes of hypothyroidism : SLC-26-A_4 gene

↓

Ⓝ Thyroid gland & innerear epithelium development

↓

encodes protein : Pendrin anion transporter

⇒ mutate SLC-24-A_4 gene

↓

defective pendrin

↓

C/f : Hypothyroidism + sensory neuronal deafness

⇒ This syndrome is called as Pendred Synd.

CLINICAL FEATURES OF HYPOTHYROIDISM

- weight gain
- ↑ BP (diastolic BP)
- cold intolerance
- loss of hair
- atherogenic profiles

Hypothyroidism in

a) Pediatric age

CRETINISM

- mental retradation
- short stature
- enlarged protruding tounge
- Umblical hernia

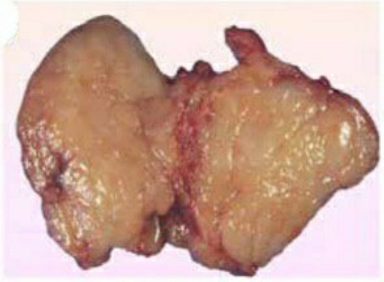
b) Adults

MYXEDEMA

- Atherogenic profile
- Loss of hair ; Alopecia
- Solid Edema (d/t mucopoly-saccharide accumul)

CLINICAL DISORDERS WITH HYPOTHYROIDISM

1. Hashimoto Thyroiditis



HASHIMOTO THYROIDITIS

Gross: diffuse and symmetric enlargement of the thyroid showing Irregular nodules and an intact capsule with pale, yellow-tan, firm, and somewhat nodular cut surface.

- A.I disease
- 40-60 yrs
- females > Males
- MCC of Hypothyroidism in Iodine-sufficient areas
- Etiopathogenesis : · a/w HLA DR-5
  · a/w gene polymorphism
  ⇓
  i) PTPN-22
  ii) Cytotoxic Lymphocyte Antigen-4 gene [CTLA-4]
- Pathogenesis : IgG Ab formed against

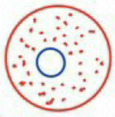
↓

TSH-R (Receptor)

↓

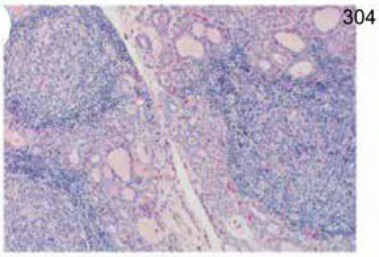
↓ T_3/T_4

- C/f : i) painless thyroid enlargement
  - ii) atherogenic profile
  - iii) Alopecia
- Diagnosis:
  - Gross : i) Diffuse symmetrical enlargement of Thyroid
  - M/E : i) Lymphoplasmacitic infiltaration
    - ↓
    - Destruction of Thyroid follicle
    - ↓
    - ii) Atrophic thyroid follicle
    - iii) Lymphocytic infiltaration with Germinal center
    - iv) Hurthle Cell (Oncocytic metaplasia)
    - ⇓
    - Hallmark of H·T



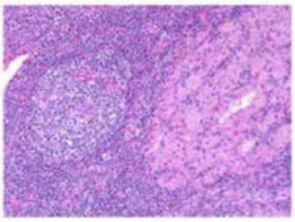
Bright Eosinophilic granular Cytoplasm

- Risks : MC a/w Lymphoma transformation (Marginal zone B Cell Lymphoma trans)



HASHIMOTO THYROIDITIS

Microscopy shows inflammatory cells form prominent lymphoid follicles with germinal centers. Residual thyroid follicles lined by epithelial cells with deeply eosinophilic, granular cytoplasm, termed Hürthle cells.

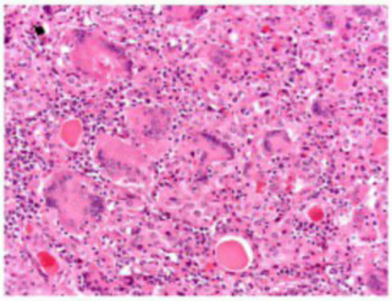


HASHIMOTO THYROIDITIS MICROSCOPY

shows inflammatory cells form prominent lymphoid follicles with germinal centers. Residual thyroid follicles lined by epithelial cells with deeply eosinophilic, granular cytoplasm, termed Hürthle cells.

2. De Quervain Thyroiditis

- aka Granulomatous Thyroiditis
- MC F>M
- a/w Viral infections : Mumps, Measles
- MCC of painful Thyroid
- M/E :
  - Neutrophilic infiltarate causing
  - ↓
  - Follicular destruction
  - Lateron Lymphocytic infiltarate
  - ↓
  - • destruction of follicle
  - • Granuloma with multinucleated giant cell → absent in H·T



GRANULOMATOUS THYROIDITIS

Thyroid parenchyma contains a chronic inflammatory infiltrate with multinucleated giant cells replacing colloid within follicle.

3. Subacute Lymphocytic Thyroiditis

- Autoimmune disorder
- F > M ; 20-40yr
- painless thyroid enlargement
- self-limiting disorder
- M/E : i) Lymphoplasmasitic infiltarate
  - ↓
  - follicular destruction

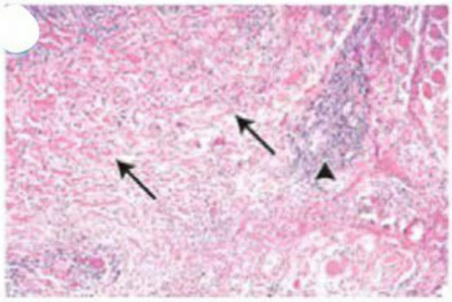
4. Reidel's Thyroiditis

- younger pt <40yrs
- Chronic inflammation + Fibrosis of Thyroid gland
- painless but "hard as wood" Thyroid
- Fibrosis involving surrounding structures like airways.

Mediastina & Retero peritoneal fibrosis

ii) Germinal Center
iii) NO FIBROSIS
NO HERTHLE CELL METAPLASIA

- They are differential diagnosis for Anaplastic Carcinoma of Thyroid
- M/E : i) Chronic inflammation
↓
destruction of follicle
ii) excessive fibrosis
(↑ collagen deposits)



RIEDEL THYROIDITIS
The thyroid parenchyma is largely replaced by dense, hyalinized fibrous tissue (arrows) and a chronic inflammatory infiltrate (arrowhead)

HYPER THYROIDISM

- Thyrotoxicosis
↓
d/t excessive activation of Sympathetic NS
+
↑ Thyroxin level

* Causes of Thyrotoxicosis
(a) Grave's disease (MC)
(b) Multinodular goiter
(c) Toxic adenoma

* C/f of Thyrotoxicosis
i) ↑ metabolism
↓
↑ Basal Metabolic rate
ii) Earliest & most consistent finding : Cardiovascular abnormality
↓
- ↑ systolic BP
- Sinus tachycardia

iii) Proximal muscle weakness
iv) Osteoporosis
v) Thyroid Storm :
- Sudden onset of severe hyperthyroidism d/t acute increase Catecholamine
- It's a/w : Stress
  Surgery
  Post-operative period
  Infections
- Commonly seen in Grave's disease
- Risk of Thyroid storm : Precipitate Fatal arrhythmia
  ∴ considered as Medical Emergency

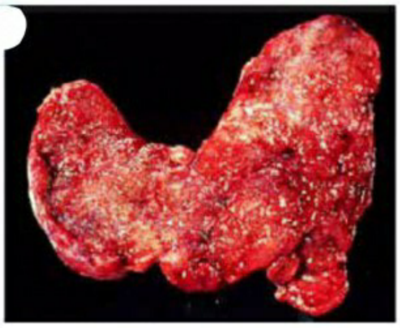
* Lab Findings of HYPERTHYROIDISM

Primary
defect in gland
↓
- T_3/T_4 ↑
- TSH ↓

Secondary
defect in Hypothalamus or pituitary
↓
- ↑ TSH
- ↑ T_3 & T_4

GRAVE'S DISEASE

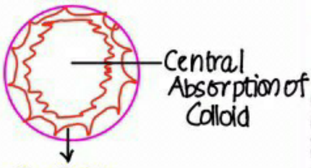
- a/w Hyperthyroidism
- A·I disorder
- F>M (20-40yrs)
- Genetics : CTLA-4 gene polymorphism
  PTPN22 gene polymorphism
- Pathogenesis :
  IgG Ab formed against TSH-R
  ↓
  Abnormal activation TSH-R
  ↓
- Lab findings : ↑ T_3 / T_4
  ↓ TSH
- Gross : Diffuse symmetric enlargement of Thyroid gland
  ⇓
  Beefy-red gross appearance



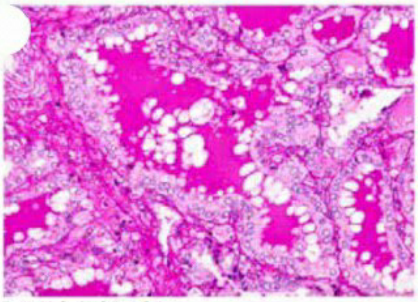
GRAVES' DISEASE

Gross shows diffuse symmetric enlargement of the gland and a beefy deep red parenchyma.

- M/E : i) Hyperplasia of colloid filled follicular cells



  ii) Scalloping of colloid
  (d/t central absorption of colloid)



GRAVES DISEASE

Microscopy shows diffusely hyperplastic thyroid follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the scalloped appearance of the edges of the colloid.

- C/f : Charachteristic Triad
  i) HYPERTHYROIDISM
  ii) INFILTRATIVE DERMOPATHY (Pre tibial Myxedema)
  iii) INFILTRATIVE OPHTALMOPATHY
  Skin of shin (over tibia) & orbital Tissue
  ⇓
  They have fibroblast with ↑ TSH-R
  ↓
  ↑ activation of TSH-R
  ↓ causes
  i) Inflammation
  ii) Fibrosis iii) Edema
  iv) ↑ accumulation of Glycosaminoglycan
  ↓
  ∴ C/f : Ex-opthalmus eye
  Pre tibial Myxedema.

GOITRE

- Thyroid gland enlargement
- MC manifestation of Thyroid gland disorders

- Pathogenesis :

Impaired synthesis of Thyroid Hormone
(↓ T_3/T_4)
↓
↑ TSH
↓
Hyperplasia of Thyroid follicle → Goitre

- 2 types of Goitre
  - a) Simple (Or) Diffuse goitre
  - b) Multinodular goitre

THYROID NEOPLASM

A) BENIGN

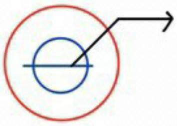
Follicular Adenoma
- Asymptomatic
- presenting with solitary cold nodules
- Herthle cell metaplasia ⊕
- No capsular & vascular invasion

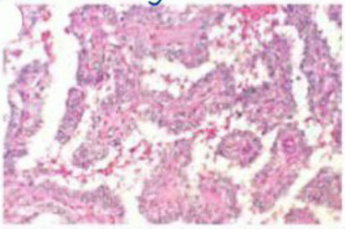
B) MALIGNANT : 4

Papillary carcinoma Thyroid (MC)
Follicular carcinoma Thyroid
Medullary carcinoma Thyroid
Anaplastic carcinoma Thyroid (Least common)

PAPILLARY CARCINOMA OF THYROID

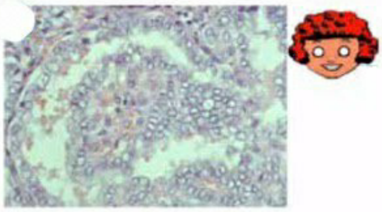
- F>M ; 20-40 yrs
- MC Type of Thyroid cancers
- Excellent prognosis with Least malignancy
- a/w Exposure to the radiation (ionising) [Head/neck]
- Genetics : • a/w Rearrangement of
  ↓
  i) RET proto oncogene
  ii) NTKR-1
  (Neurotrophic Tyrosine Kinase Receptor-1)
  • a/w BRAF & RAS mutation
- M/E : i) papillae of Tu. cells
  ↓
  Fibrovascular core
  ii) Diagnostic Nuclear finding of Tumor cell
  a) optically clear nuclei
  (orphan-annie eye app.)
  b) Nuclear grooving
  c) Pseudo inclusion
  Cytoplasmic protrusion into tumor nuclei
  iii) Psammoma Bodies





PAPILLARY CARCINOMA OF THE THYROID

Showing papillae with fibrovascular cores and classic optically clear nuclei (due to clear chromatin).
Diagnostic nuclear features are:
optically clear nuclei (orphan Annie eye like appearance)
Pseudoinclusions (arrow) and Nuclear grooving (arrowhead)



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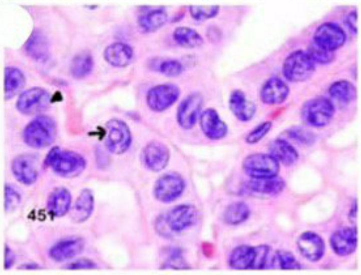


PAPILLARY CARCINOMA OF THE THYROID

Pseudoinclusions (arrow) and Nuclear grooving (arrowhead)

FOLLICULAR CARCINOMA OF THYROID

- 40-60 yrs ; F>M
- a/w Iodine deficiency
- Long standing multinodular goitre : is a risk

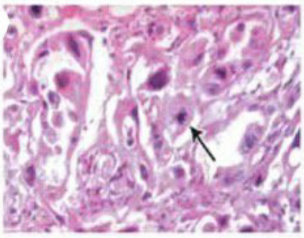
- M/E : i) ↑ small sized follicle with scanty folloid.
  - ii) Capsular & vascular invasion
- Good prognosis
- Hematogenous spread.

MEDULLARY CARCINOMA OF THYROID

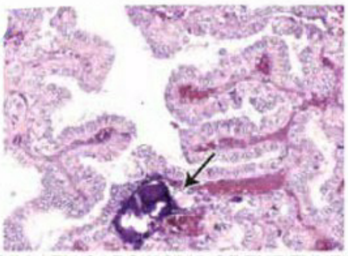
- origin : Parafollicular cells / C-Cells
  - ∴ aka C-Cell carcinoma
- can be sporadic (MC) > Familial
  - sporadic ↓
    - → Unilateral
    - → a/w : RET proto oncogene mut.
  - Familial ↓ → a/w
    - i) Von-Hippel Lindau
    - ii) Neurofibromatosis
    - iii) MEN Syndrome
    - iv) RET proto oncogene mut.
- M/E : i) Round-oval / polygonal Tumor cell
  - ii) a/w Amyloid containing stroma
    - ↓
    - d/t altered calcitonin
- Lymphatic spread is MC
- Metastases
  - MC in MEN IIB > MEN II-A

ANAPLASTIC CARCINOMA OF THYROID

- aka Undifferentiated carcinoma
- MC in elderly female
- C/f : Sudden ↑ in size of Thyroid gland
  - Dyspnea
  - Dysphagia
  - Hoarseness of voice (d/t involvement of Recurr. Laryngeal N)
- Rare tumor
- a/w Pre-exisciting Thyroid tumor
  - ↓
  - MC a/w Papillary Ca.
- Gross : involve surroung structure
- M/E : Pleomorphism of cell
  - i) Bizzare cell
  - ii) Giant cell
  - iii) Spindle cell
  - iv) Squamoid cell
- Least common type
- Worst prognosis

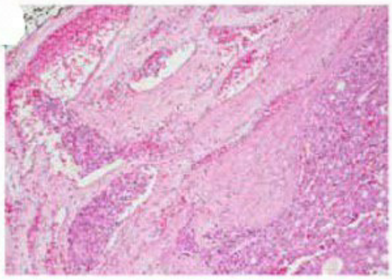


ANAPLASTIC CARCINOMA OF THE THYROID



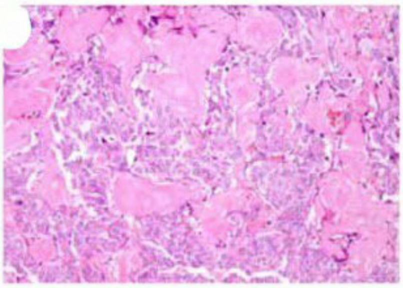
PAPILLARY CARCINOMA OF THE THYROID

Showing papillae with fibrovascular cores and classic optically clear nuclei (due to clear chromatin) with calcified Psammoma bodies.



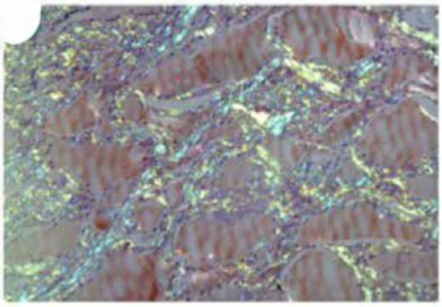
FOLLICULAR CARCINOMA OF THYROID

Vascular or capsular invasion is hallmark in the diagnosis of follicular carcinoma. Vascular invasion is seen here as tumor cells present within a large capsular blood vessel.



MEDULLARY THYROID CARCINOMA

The tumor features nests of polygonal cells embedded in a collagenous framework. The connective tissue septa contain extracellular eosinophilic amyloid.

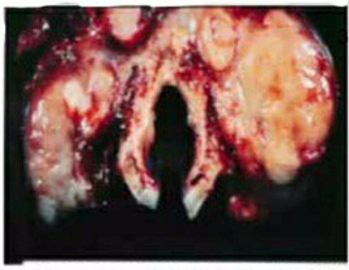


MEDULLARY THYROID CARCINOMA

Congo red staining under polarized light demonstrates the apple green birefringence of amyloid.

DIABETES

- Disorder of hyperglycemia d/t i. insulin defect
  either action & secretion



ANAPLASTIC CARCINOMA OF THE THYROID

The tumor in transverse section partially surrounds the trachea and extends into the adjacent soft tissue.

- INSULIN
  - Synthesized by : β- islets of pancreas.
  - β- cells

↓

E.R = Store inactive form of insulin (Pro- insulin)

↓

Pro-insulin transffered into Golgi- Bodies

↓

Breakdown in Golgibodies into

INSULIN

- anabolic hormone as Insulin

↓ ⊕

GLUT-4 on Skeletal ms
Adipose tissue

↓

↑ glucose uptake into tissue
↓ sr. glucose

↓

↑ glycogen synthesis
↑ lipid synthesis
↑ protein synthesis

C-PEPTIDE

- marker of endogenous insulin secretion
- can differentia Type I & Type -II DM

Type I → β- cell destruction → ∴ ↓ c - peptide

Type -II → β-cells normal → ∴ normal C-peptide

Glycosylated Hb (HbA_{1c})

- Formed by non-enzymatic combination of glucose with globin of Hb
- Clinical significance
  - (i) Monitor Blood glucose level for past 8-12 weeks
  - (ii) Diagnosis of DM
- Interpretation

Normal : <5.7%
pre DM : 5.7-6.4%
DM : ≥6.5%
Target HbA_{1c} : <7%

EUGLYCEMIA:

Plasma glucose level (mg/dl)
i) Fasting glucose : <100 mg/dl
ii) 2hrs OGTT : <140 mg/dl
iii) HbA_{1c} : <5.7%

IMPAIRED GLUCOSE TOLERANCE

- prediabetic patient

i) Fasting glucose : 100-125 mg/dl
ii) 2hrs OGTT : 140-199 mg/dl
iii) HbA_{1c} : 5.7-6.4%

DIAGNOSIS OF DM :

Signs & symptoms : Polydypsia
Polyuria
Polyphagia

i) Fasting glucose : >126 mg/dl
ii) 2hrs OGTT : >200 mg/dl
iii) HbA_{1c} : ≥6.5%
(iv) Random Blood glucose : >200 mg/dl

CLASSIFICATION OF DM

1) Type -1 DM
2) Type -2 DM
3) Type - 1.5 DM / Type-3 DM
4) MODY : Maturity onset Diabetes of Young
   i) MODY 1/2/3/4/5 ...
   ii) Maternally inherited Diabetes with deafness d/t mitochondrial DNA mutation
5) a/w Pancreatic defect
   Eg : Chronic pancreatitis
   Hemochromatosis
   Cystic fibrosis
6) a/w Endocrinopathies
   i) Cushing's syndrome
   ii) GH adenoma
   iii) Hyperthyroidism
7) a/w Infections
   i) Measles
   ii) Mumps
   iii) Cox-sackie virus
   iv) CMV

TYPE-1 DM

- usually children (<20 yrs)
- Thin physique
- Auto immune disorder d/t β-islet cell damage

↓

Absolute deficiency of Insulin

- Less common ; Only 10%
- Pathogenesis : A·I disorders

Genetic Factors

MHC Genes
* mc a/w MHC-II gene
  - DR-3/DR-4
  - DQ-8
    ↓
    Greatest Inherited risk

Non MHC Genes
* mc a/w PTPN 22 gene polymorphism
* CTLA-4 polymorphism

Enviornmental Factor
↓ Molecular mimicry
Viral infection
↓ ⊕
CD$_8$ T cell
↓
Killing/destruction of β-cells

- Mechanism :
  Hyperglycemia & Ketosis : When >90% of β-cell damage is there

β-cell damage
↓ d/t

1. Inflammation
   CD$_4$ T cell
   ↓ release
   IFN-γ/TNF-α
   ↓
   damage of β

   CD$_8$ T Cell
   ↓
   direct destruction of β-cell

2. Auto antibodies formed against β-cells & insulin
   ↓
   Ag are
   i) Glutamic acid decarboxylase (MC)
   ii) Insulin cell Ag-512 (ICA-512)

TYPE-2 DM

- MC type of DM ; >80% of cases
- Not an A.I disease

- Patient older & obese
- Multifactorial involvement

(A) GENETICS

* polymorphism of TCF-7-L-2 gene (transcription Factor 7 like 2 gene)

B) Enviornmental Factors

i) Obesity
ii) Sedentary lifestyle
iii) Dietary Habits

⇒ β-cells is normal : ↑ insulin secretion
Insulin Resistance

- Metabolic defects :

(a) INSULIN RESISTANCE | (b) β-CELL DYSFUNCTION

- Definition : Decreased response of peripheral tissue to insulin.
- Factors responsible for Insulin Resistance : Most important Factor
↓
CENTRAL OBESITY

- Mechanism of insulin resistance

1) Increased amount of Free Fatty Facity
a/w Obesity → ↑ FFA goes to
↓
Tissue (liver/muscle)
↓
Converted to Intracellular Triglycerides
↓
Undergo FA oxidation
↓
Formation of toxic substances like
Eg : Diacyl Glycerol
Ceramide
↓
Inhibit insulin signalling → Insulin Resistance

2) d/t Adipokines

Under Normal condition : Adipose tissue is considered as Functional Endocrine gland.

Adipose tissue ⟶ secretes Adipokines

Pro hyperglycemic Adipokines
Eg: (i) Resistin
(ii) RBP-4
(Retinol Binding protein-4)

Anti-hyperglycemic Adipokines
Eg: Leptin
Adiponectin

⇒ In obese : ↓ adiponectin → Insulin resistance

3) Inflammation : FFA within Mac/β-cells
↓ ⊕
Inflammasomes
↓
release IL-1β → Insulin Resistance

4) Peroxisome Proliferated Activator Receptor-γ-mutation (PPAR-γ)

PPAR-γ is a nuclear receptor

- (i) Activates Adiponectin
  - ↓ glucose
- (ii) FFA deposition into Adipose tissue (not in Liver/muscle)

⇒ mutation in PPAR-γ → Insulin Resistance

also a/w Monogenic diabetes

(b) B-CELL DYSFUNCTION

1. ↑ FFA ⟶ damage of β-cell
2. Amyloidosis ⟶ damage of β-cell (only in Type-2)
3. Abnormal INCRETIN HORMONE

Normal INCRETIN by Intestine
- a) activate insulin
- b) glucagon

⇒ In obese individual → Abnormal incretin → β-cell dysfunction

TYPE 1·5 DM

- aka Type 3 DM
- considered as Variant of Type I DM
- A·I origin
  aka Latent Auto immune Diabetes of Adults - LADA
- These are slow onset diabetes & require Insulin T/t·
- with controlled blood sugar ∴ CVS abnormality ↓ red

MONOGENIC DIABETES

- These are uncommon diabetes
- Causes : (i) Genetic defect in β-cell function
  - Hereditary ; AD
  - younger pt (<25yrs) or Neonatal
  - not a/w i) β-cell autoantibodies
    ii) obesity
  - Eg: 1. MODY (MC form)
    2. Maternally inherited Diabetes & deafness (d/t mitochondrial DNA mutation)

  (ii) Defective insulin action
  - mutations in gene regulating
    - Insulin Resistance
    - Insulin Signalling

COMPLICATION OF DIABETES

ACUTE COMPLICATION

i) Polydypsia, Polyphagia
Polyuria

ii) Diabetic Keto acidosis (DKA)

- MC a/w Type-1 DM (absolute deficiency of insulin)

Insulin ──⊖→ Lipolysis & Ketone Body formation

- Mechanism :

↓insulin + ↑counter regulatory hormone
Eg: GH/Catecholamines/ACTH

Release of FFA from adipose tissue
↓
goes to LIVER
↓
FA oxidation
↓
↑Ketone body formation
↓
Metabolic acidosis

- Blood glucose level : 250-600 mg/dl
- Osmotic diuresis ⟶ Dehydration
- Clinical Presentation : i) Thirsty
  - ii) Nausea, Vomitting
  - iii) Abdominal pain
  - iv) Laboured breathing/ Gasping breathing ⇒ Kussmaul's Breathing } In sever DKA
  - v) Fruity breath odour (d/t Acetone) } In sever DKA

iii) HYPER OSMOLAR HYPER GLYCEMIC STATE (HHS)

- MC a/w Type II def (Insulin resistance)
- Pathogenesis : Insulin ⟶ ⊖ Lipolysis → No Ketone Body formation

↓insulin + ↑counter regulatory hormone

Hyperglycemia (600-1200 mg/dl)
↓
Severe Osmotic diuresis
↓
Dehydration
↓
Coma
↓
Death

- Mortality rate is higher in HHS > DKA
- Triad :
  - Hyperglycemia
  - Hyperosmolality (330-380 mOsm/kg)
  - Dehydration without Ketoacidosis

CHRONIC COMPLICATION

a) Non enzymatic glycation of Vascular Basement Membrane can lead to i) Diabetic Retinopathy

ii) Diabetic Nephropathy
iii) M.I (MCC of death)
iv) Neuropathy

b) Osmotic damage
Glucose ⟶ Sorbitol & enters into Schwann cell
i) Peripheral neuropathy
ii) Cataract.

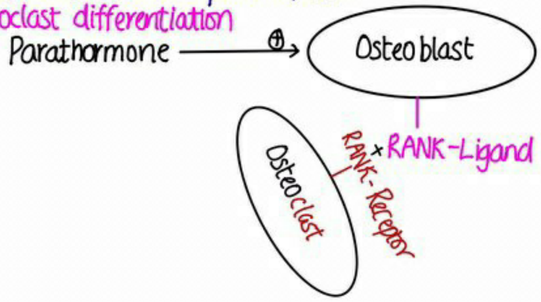
PARATHYROID GLAND

- consit of
  - A) Chief Cell
    - consisting of parathormone
  - B) Oxyphil Cells
    - consist of glycogen

# colloid filled follicular cells are also present
↓
Glycogen ⊕
Ca-oxalate crystal ⊖

- Parathyroid Gland Function controlled by: Free serum Ca^{2+} level.

↓
Release Parathormone:
- ↑ Sr. calcium
- ↑ Urinary phosphate excretion
- ↑ Gastrointestinal absorption of Ca^{2+}
- Osteoclast differentiation



HYPER PARATHYROIDISM

A) Primary

- MC a/w Parathyroid Adenoma
- a/w Parathyroid hyperplasia
- ↑ PTH → ↑ Ca^{2+} & ↓ Sr. PO_4^{2-} & ↑ urinary PO_4^{2-} excretion
- C/f :
  - Nephrocalcinosis
  - Oxalate crystal Formation
  - Neuropsychiatric Manifestation
  - Brown's Tumor / Reckling hausen disease or Osteitis fibrosa cystica
    ⇓
    Cysts in jaw bone : ↑ osteoclast with hemosidderin (d/t hemorrhage

B) Secondary

- In chronic Renal Failure
  ↓ Sr. Ca^{2+} & ↓ PO_4^{2-}
  ↓
  ↑ PTH

HYPO PARATHYROIDISM

- Lab findings : $\downarrow$PTH → $\downarrow$ Sr. Ca^{2+} , $\uparrow$ Sr PO_4^{2-}
- Causes : i. MCC : Surgical excision
  - ii. Irradiation
  - iii. Digeorge syndrome
- C/f : · Hypocalcemia
  - · Tetany : 2 Signs
    - Chvostek
      - Tap the facial muscle of cheek (supplied by facial N.)
      - ↓
      - Facial muscle contraction
    - Trossau-Sign
      - during BP measurement
      - ↓
      - Cuff causes obstruction of Brachial artery
      - ↓
      - Carpal Spasm

ADRENAL GLAND

- consist of 2 part
  - Cortex
    - a) Zona Glomerulosa : Release Aldosterone/ Mineralocorticoids
    - b) Zona Fasciculata : Release Glucocorticoids/ Cortisol
    - c) Zona Reticularis : Release Androgens / Sexhormones
  - Medulla
    - * consisting of Chromaffin Cells
      - ↓
      - These are neural crest derived cells
    - * release catecholamine & it's products i.e
      - · Epinephrine
      - · Nor-epinephrine

HYPO ADRENALISM

- Primary
  - * gland is defective
    - Acute
      - i) steroid withdrawal
      - ii) Stress
      - iii) Infections
        - Eg: Neisseria Meningitis
        - ↓ cause
        - Adrenal Hemorrhage
        - (↓BP → Shock → Death)
        - } Waterhouse Friedrichsen Syndrome
    - Chronic
      - * Addison's disease
- Secondary
  - * pituitary/hypothalamus defective
  - * skin hyperpigmentation ⊖

ADDISON'S DISEASE

- Features of 1° Hypoadrenalism
  - ↓ Aldosterone → Hyponatremia → ↓Na⁺ → Hypotension; ↑ K⁺ → Met. Acidosis
  - ↓ cortisol → Hypoglycemia
  - ↑ACTH → pro-opiomelanotropin → ↑ melanin → Hyper pigmentation
- seen when >90% of adrenal cortex is damaged
- causes:
  1. MCC : Autoimmune Adrenalitis. (MC in world)
  2. Tuberculosis (MC in India)
  3. ↓ Na⁺ / Hypotension
  4. Hyperpigmentation
  5. Hypoglycemia
  6. Weackness

2° Adreno insufficiency

⇒ defect in hypothalamus / Pitutary → ↓ACTH → No hyperpigmentation

⇒ Causes :
- i) infections
- ii) infarctions
- iii) radiations

HYPER ADRENALISM

- ↑ Hormone from Adrenal cortex
  1. Glomerulosa effected → ↑aldosterone → Hyper aldosteronism
  2. Fasciculata effected → ↑ Glucocorticoids → Cushing's Syndrome
  3. Reticularis effected → ↑ sex hormones → Adreno genital Syndrome

HYPER ALDOSTERONISM

- ↑ aldosterone → ↑ Na⁺ → ↑ plasma expansion → Hypertension
- ↑ aldosterone → ↓ K⁺ → Metabolic alkalosis
- can be
  - A) Primary
    - Adrenal adenoma : MCC
    - Adrenal hyperplasia
    - Adrenal carcinoma
  - B) Secondary
    - CRF
    - CHF
    - Cirrhosis

CUSHING'S SYNDROME

- ↑ glucocorticoids/cortisol
- causes :

(i) Exogenous steroid T/t ↓ MCC of cushing synd.

(ii) Pituitary Causes ↓ * Pituitary adenoma (MC)

(iii) Adrenal a/w ↓ * Adrenal Adenoma

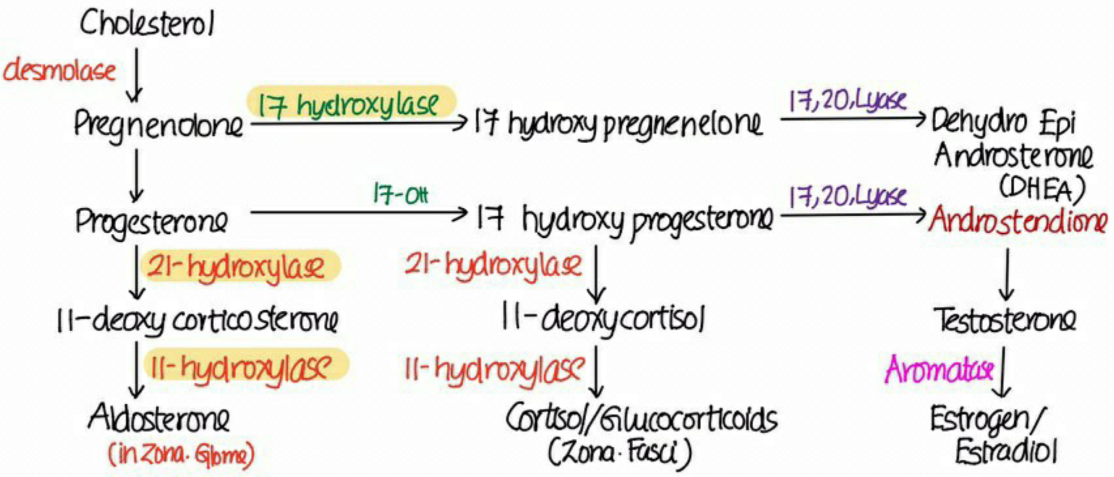
(iv) Paraneoplastic ↓ * d/t ectopic ACTH ↓ MCC Carcinoid > Small cell Ca. Lung

- C/f :
  - muscele wasting (↑ cortisol → ↑ muscle breakdown)
  - Moon facies
  - Buffalo hump
  - Abdominal striae
  - Hypotension & osteoporosis

ADRENOGENITAL SYNDROME

- aka Congenital Adrenal Hyperplasia (CAH)
- Enzyme deficiency → Defective Adrenal cortex Hormone synthesis ↓ ↓Mineralo/cortisol/Sex hormone
- C/f :
  - Electrolyte imbalance
  - Glucose metabolism
  - Sexual differentiation defective

ADRENAL STEROID & CAH

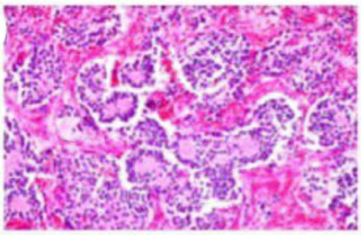


3types of Adrenogenital Syndrome

17-OH deficiency	21-OH deficiency (MCC)	11-OH deficiency
* ↓androgen ↑ mineralocorticoids * C/f: Male · Undescented testis · Ambigous genitilia * C/f : Female · No 2° sexual development	* Androgen ↑ Mineralocorticoids ↓ Glucacorticoids ↓ * C/f : Infants · salt wasting * C/f : Children · Precocious puberty * C/f : Females · Virilisation	* ↑ androgen ↓ Aldosterone ↓ cortisol * C/f : Female · Virilisation

ADRENAL MEDULLA TUMOR

- MC Tumor : PEDIATRIC : Neuroblastoma
  ADULTS : Pheochromocytoma
- Neuroblastoma
  - origin : Neural crest cells
  - MC <5yr (peack age group 1.5yrs)
  - MC presentation : Abdominal mass
  - Opsoclonus & Myoclonus : Paraneoplastic synd.
    (Dancing Eye / Dancing Feet)
  - Sporadic cases a/w NF-1 gene mutation
  - Lab Finding : · Bombesan +
    - Synaptophysis +
    - Chromogranin +
    - Urine : ↑ VMA & other catecholamine metabolites
  - M/E : · small round blue cell tumor
    - Homer wright pseudo rosette



NEUROBLASTOMA

Showing small, round blue tumor cells with faintly eosinophilic fibrillary material (neuropil) that corresponds to neuritic processes of the primitive neuroblasts. Typical Homer-Wright pseudorosettes are seen, in which the tumor cells are concentrically arranged about a central space filled with neuropil.

  - Prognosis :

# good	# Bad
· Gangliocytic differentiation & schwannomian stroma	· Absent
· Intra tumoral Calcification ⊕	· Absent
· Hyperdiploidy	· Diploidy
· N-myc amplification ⊖	· present
· TRK-A ⊕	· TRK-B ⊕
· Serum Ferritin : Normal	· Elevated
· Serum LDH : Normal	· Elevated

  - MC site for metastases : Lymph Node > Bone marrow

Pheochromocytoma

- origin : Chromaffin Cells
  if it's extra adrenal origin : Paraganglioma
- MC These are Benign tumors
- a/w Succinate Dehydrogenase mutation
  Von - Hippel Lindau synd.
  NF-1
- Follow Rule of 10% i.e
  10% Malignant
  10% Bilateral
  10% Familia
  10% Extraadrenal
  10% pediatric
- C/F :
  - Episodic release of Epinephrine / NE
    ⇓
    Episodic HTN
  - Episodic Hyperadrenergic symptoms
    i.e pain, pressure, palpitation
- M/E :
  - Salt-pepper chromatin
  - Eosinophilic granular cytoplasm
  - Tumor cells are called Chief cell
    - positive for Synaptophysin
      Chromogranin
    - S-100 −ve
  - Chief cells arranged in cluster of balls calledas Zell ballen pattern
  - Two Zell ballen are seperated by fibrous septa
    ↓
    Contain Substentacular cell (S100 +)
  - Immunophenotyping
    CD56 / 57 58 +ve
    CD10 +
  - Urine examination : ↑ VMA
    ↑ Metanephrin / Epinephrin

Multiple Endocrine Neoplasia (MEN)-Synd

- Younger
- Hereditary / AD ⇒ gp of disorder
  ⇓
  Hyperplasia of Endocrinal organ ⟶ Tumor/malignancy
- It's of 4 types
  - MEN-I / Wermer Syndrome
    - a/w MEN-1 gene mutation
    - Consist of
      (i) Pituitary adenoma
      (ii) Parathyroid hyperplasia
      (iii) Hyperplasia, Adenoma, Carcinoma of pancreas
      (iv) Carcinoid
      (v) Gastrinoma
  - MEN-II / IIa / Sipple Syndrome
    - a/w Medullary carcinoma of Thyroid
      Pheochromocytoma
    - Parathyroid hyperplasia > Adenoma
  - MEN-III / II_B / Gorlin Syndrome
    - consist of Medullary ca of thyroid
      Pheochromocytoma
    - a/w Marfhoid habitus
      Mucosal neuromas
  - MEN-IV
    - d/t CDKN1B gene mutation
    - Parathyroid / pitutary adenoma
    - Adrenal & Testicular Tumors
- In general They are aggressive

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